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Review

Principles and Application of Ultrasound in Pharmaceutical Powder Compression

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The use of ultrasound during the tableting of pharmaceutical powders is a new concept. However, in the metallurgy, plastic, and ceramic industries, ultrasound-assisted compression of materials has been known for some years. Ultrasound improves the characteristics of the compression process leading to optimized mechanical strength of the compacts without applying excessive compression force. Therefore, problems associated with high-pressure compression in tableting can be overcome and tablets may be manufactured more economically and consistently with the aid of ultrasound compared to conventional pressure processes. Although great progress in the theoretical understanding of the ultrasound-assisted powder compression process has been made since the late 1960s, the need for further research in the area of ultrasound application during pharmaceutical powder compression is essential. Further investigations on a wide range of drugs and excipients, to expand the usefulness and scope of the ultrasound-assisted technique, and to understand the complex phenomena involved in the process, are needed. In this article the principles, advantages, and limitations of the application of ultrasonic vibrations during pharmaceutical powder compression is reviewed with the hope that this article can contribute to, and stimulate research in the area.

KEY WORDS: compression; ultrasound; pharmaceutical powder compression; tableting.

INTRODUCTION

Tablets are the most widely used dosage forms owing to such advantages as, simple but accurate administration, rapid and simple means of mass production, and, easy storage, packaging, and dispensing (1,2). Tablets of various types and biopharmaceutical properties are produced by compression of the powder formulation.

Although the compression process may seem a simple mechanical operation, it is highly complex and problems, such as low tablet strength, capping, sticking, and limited use of direct compression, are common in large-scale production of tablets (3). There is a demand for high-speed mass production of medicinal tablets which requires the process of powder compression to be closely studied with a view to possible improvement. Early approaches have focused on evaluation and improvement of various mechanical means of tableting. Significant improvements have been made in the design of rotary machines and also to the tableting process (4). In addition, due to an ever-increasing variety of pharmaceutical products, the need to reduce the preformulation period, and the demand for higher quality products, careful and in depth studies of the mechanism of powder compression have been carried out. This has coincided with demands for efficient production in the fields of powder metallurgy, the plastic industries, and dry-pressing in the ceramic industry. As a result, there has been a stimulus for fundamental research into the compaction of powders, with contributions from all these industries (5–7).

Successful methods of compact production are attained when optimum mechanical strength is achieved without applying excessive compression force. The application of ultrasound during powder compression is one novel method of achieving this. Problems associated with high compression pressure may be overcome and tablets may be manufactured more economically and more consistently with ultrasound than by conventional pressure processes. Although the concept of ultrasound application during the tableting of pharmaceutical materials may be recent, ultrasound-assisted powder compression in metallurgy, plastic, and ceramic industries has been used for many years.

POWDER COMPRESSION PROCESS AND PROBLEMS IN TABLET MANUFACTURE

Normally a tablet is formed by the compression of a powder mass between two punches within the confines of a die into a single coherent unit. During compression, the ability of a powder to decrease in volume under an applied pressure (compactability) occurs partly as a result of displacement of the gaseous phase. Consolidation, which is an increase in the mechanical strength of the compact due to plastic flow and particle-particle interactions leading to bond formation, is coincidental with this process. Hence, the compression of a powder is the compaction and consolidation of powder particles into a tablet of specified strength. The series of events that occur in the

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process of compression and ejection of a tablet are: transitional repacking of powders, deformation of particles at points of contact, fragmentation of brittle particles, bonding between particles, deformation of the solid body, decompression due to elastic recovery, and ejection of the tablet (8).

All pharmaceutical materials do not undergo compaction and consolidation during tableting to produce coherent tablets. Poor compressibility of pharmaceutical powders is one of the main causes of tablet defect. These tablets fail the required standards and are rejected. These imperfections may be due to one or more of the following: low crushing strength, binding, sticking, filming, picking, capping, lamination, chipping, and cracking. Parameters that have been shown to exert an effect on the production of a uniform tablet may be classified according to material properties (crystal form, particle size and shape, plastic or elastic nature), machine variables, and environmental factors. Comprehensive studies and overviews of these factors, which are out of the scope of this review, are found in the literature. In this article, the principle and possible applications of ultrasound during pharmaceutical tablet production, with a view to assist compression of poorly compressible materials, are examined.

ULTRASONICS

Ultrasonics is the term usually used to refer to the generation, transmission, and reception of energy in the form of sound waves which are propagated at a frequency above the highest frequency that can be detected by the human ear (9). Considering 18 kHz as an approximate limit of human hearing, ultrasound refers to sound above 18 kHz. This range of frequencies is quite attractive for industrial applications because of the absence of noise.

Ultrasonic waves are of precisely the same nature as sound waves and their propagation and absorption in various media are governed by the laws which apply to sound transmission (10–13). Ultrasonic applications can be classified as being either low or high intensity. At low intensities, ultrasound is used as a means of investigating structural properties of materials. In this case, the material under study does not suffer any permanent change in its structural and chemical properties. Many low-intensity applications are made at very high frequencies; typically in the mega-hertz range. At high intensities, ultrasound is generally used for changing the properties of the material through which it is passed (11). The changes brought about by high-intensity ultrasound are often permanent. High-intensity applications are nearly always made at low frequencies, often just above the audible limit (12). Such waves are widely used for cleaning, plastic welding, drilling, metal bending, foam extrusion, and powder compression.

High-Intensity Ultrasound

In the strictest sense, all applications of high-intensity ultrasonic energy are based upon the mechanical effects which result from particle motion. Various mechanisms may be activated by the ultrasonic energy to promote the effect on media, but the mechanisms involved are not always known or understood. Most of these effects may be related to (14):

- Heat: As ultrasound progresses through a medium, energy is lost to the medium in the form of heat. At certain interfaces, energy absorption may be high because of shear (friction) across the interface. In addition, the amount of energy converted to heat is directly proportional to the amplitude of ultrasonic vibration (15).
- Stirring: Intense ultrasound will produce violent agitation in dispersed material by accelerating the random motion of the particles in the material.
- Chemical effects: Chemical activity, especially oxidation reactions, may be accelerated. This has been attributed to the heat that is generated and also to stress-associated molecular breakdown. Ultrasound has been reported to promote polymerisation or de-polymerisation (16) depending upon the nature of the molecules being treated.
- Mechanical effects: Stresses developed in an ultrasonic field can cause ruptures in materials and severe erosion of surfaces. They may also cause relative motion between surfaces, which produce selective absorption at the particle surfaces (17).
- Cleansing: Sometimes a protective coating is removed acoustically from a surface which will allow reactions between two materials that would not be possible otherwise.

In terms of pharmaceutical powder compression high-intensity ultrasound is used and a number of the above mechanisms may be involved to aid the production of a coherent compact.

Principles and Procedures of Ultrasound Application

Power output, amplitude, and frequency of the ultrasound used vary from application to application. Watson, 1988 (18) classified the high power ultrasonics into two main frequency bands; 20 to 22.5 kHz and 35 to 40 kHz. The frequency of 20 kHz has been the industry standard for some 30 years though a newer complementary band of 35 to 40 kHz has been emerging over the last 15 years. However, other frequency ranges have also been used to assist powder compaction process, such as 10 to 20 kHz (19), 10 to 100 kHz (20), and 1 kHz to 2 MHz (21).

The amplitude of the ultrasound used in powder compaction has been typically up to 60 μm (20,22–23); however, amplitudes as high as 125 μm has been used in the moulding of polymers (24).

Various modes of ultrasound vibration has been used for different applications, although most commonly longitudinal, others such as tortional, radial or a combination have also been used. Tsujino and Ueoka (1979) (25) applied ultrasonic vibration, when upper and lower punches were driven in longitudinal vibrational mode, and a die was driven in longitudinal, tortional, and radial vibrational modes to compact metal powders.

Ultrasound-assisted compression equipment and procedures may be different, depending upon the kind of material handled and the desired characteristics of the finished compacts. Although differing in the design and circuitry, all ultrasonic compression rigs contain the following basic components (Fig. 1):

i. The generator is an electrical high-frequency unit, which converts conventional 50 to 60 Hz electrical input into a high frequency alternating electrical output in the ultrasonic range of 20 to 50 kHz. The actual operating frequency of the generator

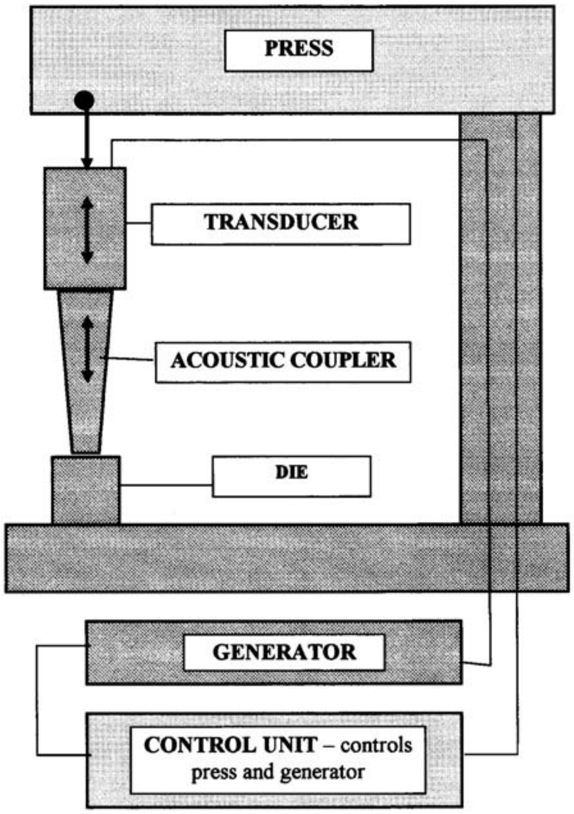

Fig. 1. Schematic diagram of an ultrasonic compression rig.

is dictated by the mechanical resonant frequency of the transducer and coupler. Outputs may vary from 50 watts to several kilowatts as required.

ii. The transducer converts the high-frequency electrical output of the generator into high-frequency mechanical vibrations. This is the basic element in any ultrasonic system which converts energy from one form to another. Two types of materials are used for the conversion of electrical into mechanical oscillations; piezomagnetic or "magnetostrictive" (metals) and piezoelectric materials (special ceramic materials).

Piezomagnetic transducers are made from a number of magnetic materials e.g., pure nickel and iron-cobalt alloys (11), that deform as a result of an applied magnetic field. Piezomagnetic transducers are not commonly used today in high-intensity ultrasound due to their poor electro-acoustic transfer efficiency (dissipates about 70% of the energy as heat) (26). Moreover, a piezomagnetic converter usually requires liquid cooling which is not cost effective (18).

Piezoelectric materials deform under the influence of an electric alternating field (11–13,17). When an alternating voltage is applied to the opposing faces of a disc of piezoelectric material, the disc expands and contracts with the repeated change of polarity. In industry ceramic transducers are normally used (11,17,27). A common type of ceramic transducer is a sandwich transducer, where a piece or pieces, of fragile piezoelectric material is cemented between two plates of non-piezoelectric material (18). Piezoelectric oscillators are low in cost and very efficient, with a typical maximum efficiency of 95% or above (28). Therefore, for high-output ultrasonic applications, including powder compression, the piezoelectric transducer is almost exclusively used.

iii. The acoustic coupler focuses, amplifies and transmits the mechanical vibrations from the transducer to the powder in the die. Other expressions commonly used when referring to an acoustic coupler are "horn," "stub," "sonotrode" or "velocity transformer."

A horn is attached to the transducer and has three main functions when used for ultrasound-assisted powder compression: (i) to deliver ultrasonic vibrations to the material, (ii) to increase amplitude to a usable level which is limited to 4.5 fold, and (iii) to apply pressure to the powder to form the compact.

Ideally, the material used for a coupler should have good acoustic properties, a high fatigue strength, low acoustic loss, and low density. For most applications it should be corrosion- and erosion-resistant, quite hard, and not expensive (14) and therefore, most horns are made of either high strength aluminium or titanium alloy, often with a hard-coated working face (28,29).

The vibration amplitude at the radiating surface depends upon the geometry of the coupler, its energy losses and the vibration amplitude at the driven end. To increase the vibration amplitude it is necessary for the horn cross-section to be narrower towards the work piece. There are two basic designs of acoustic couplers used for production purposes, the exponential coupler (Fig. 2a) and the stepped coupler (Fig. 2b). Both types of horns produce displacement amplification; i.e., the vibration amplitude at resonance is greater at the small end of the coupler than at its larger end.

Amplitude transformation for an exponential coupler is given by the ratio of the end diameters D/d, but for ratios >3 the stepped coupler is used. For the stepped horn, the amplification factor is given by the ratio of the ends areas, i.e., $(D/d)^2$. Maximum displacement is obtained at the tip of the coupler when the resonance frequencies of the transducer and the horn are the same.

The transducers and acoustic couplers are designed to resonate at a predetermined frequency and therefore they are usually one half-wavelength long (11).

Ultrasound-Assisted Powder Compression

Ultrasound-Assisted Compression of Metal Powders

This has allowed a reduction in the static load, temperature, and compaction time (30–31). It has been found that use of sonic vibrations (10–20 kHz) for the formation of metal compacts improved both their density (19) and mechanical strength (36). The use of ultrasonic vibration during metal powder compaction induces bulk particle movement, resulting in an increase in the densification and uniformity in the structure of the compacted material (37–38).

Ultrasound-Assisted Compaction of Ceramic Powders

Ceramics are brittle materials, in which fracture generally occurs by the propagation of pre-existing flows or microcracks. The quality of the product is highly dependent on the processes of fabrication, especially before firing. Therefore ultrasound has been used to assist the pressure during the powder compression stage in order to; decrease the number of pre-existing

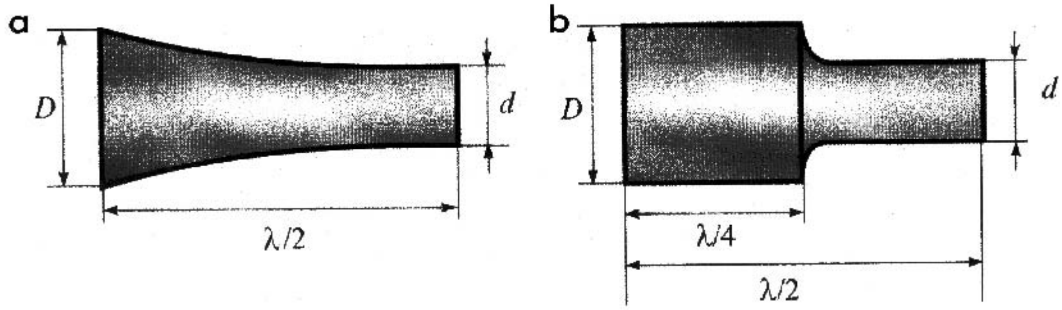

Fig. 2. Basic designs of acoustic couplers; a) exponential coupler b) stepped coupler.

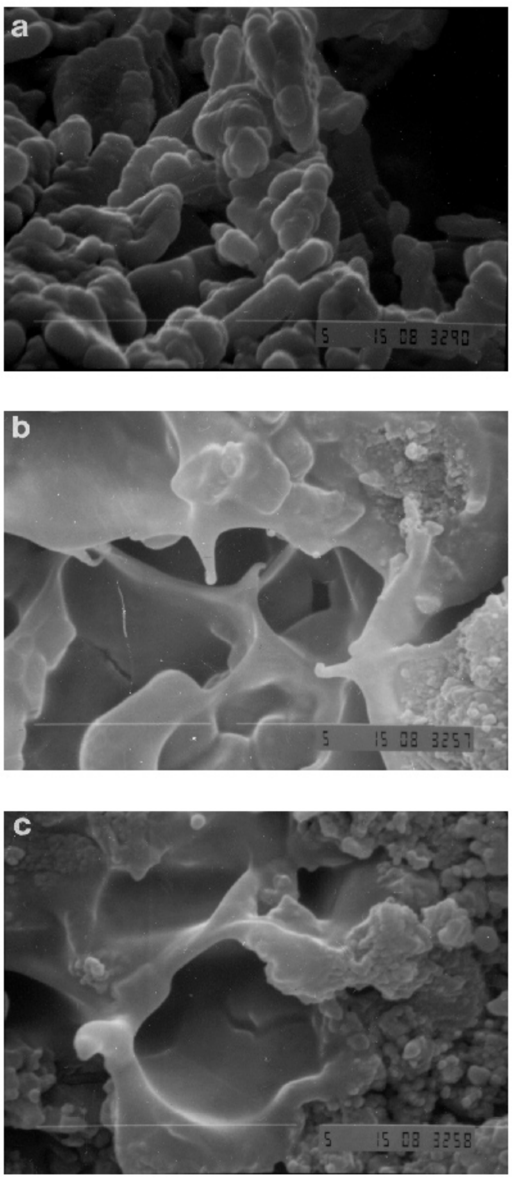

Fig. 3. Scanning electron micrographs of the upper surfaces of paracetamol tablets containing 10%w/w of PVP compressed at 32 MPa without ultrasound (a) magnified at X5000 and with ultrasound (b) magnified at X5000, (c) magnified at X7500.

defects (22), decrease the porosity (39), increase compact density (23,40), increase compact hardness (41) and decrease the force of compaction (42).

Ultrasound-Assisted Compaction Moulding of Polymer Powders

This has offered a number of advantages over the conventional methods (32–35). These methods include, fast and cost effective manufacturing processes without the use of external heat sources, and compaction moulding of high molecular weight polymers, which are difficult to mould by conventional methods due to their high melt viscosity.

The ease with which thermoplastic materials can be moulded by ultrasound depends primarily on the ability of the material to pass on the ultrasonic energy, i.e., its damping properties (43). Other important parameters are the plastification temperature range with amorphous and the crystallite melting points, the density, the moduli of dynamic elasticity and shear, the velocity of the sound, and the resultant wave length (43).

Ultrasound-Assisted Compression of Pharmaceutical Powders

Although high-power ultrasonic vibration has been used for many years to assist the compression of metallic, ceramic or plastic materials, in pharmaceutical technology only few papers are reported, and the first one dates back to 1993 (20), despite the promising results that have been obtained. Therefore, ultrasound is still a novel method to assist the compression of powders in pharmaceutical industry.

Gueret (1993) (20) applied ultrasound simultaneously with mechanical pressure to assist the compression of pharmaceutical and cosmetic preparations. He used powder mixtures containing from 5 to 80 %w/w of at least one thermoplastic material, such as polyethylene, polystyrene, polyamides, polyvinyl chloride and poly(ethylene terephthalate). The remainder composed of at least one non-thermoplastic mineral or organic substance. It was found that the presence of a thermoplastic product in the formulation allowed the formation of a framework that held the non-thermoplastic powders together. The following parameters were used to produce thin friable compacts at lower compaction pressures: frequency = 10–100 kHz; amplitude = 20–60 μm; power = 1–3 kW per cm^3 of compact; ultrasound duration = 0.25–3 seconds; pressure = 4–20 MPa (19).

Before giving examples and the advantages, limitations and the future of this technique, it would be appropriate to look first at the mechanisms involved during ultrasound-assisted compression of pharmaceutical powders.

Physics of the Ultrasound-Assisted Compression Process

A combination of vibratory compaction and dynamic consolidation would add a new dimension to conventional compression techniques and allow for the development of new products with new properties (44). However, the lack of systematic knowledge and fundamental understanding of the underlying physics of the ultrasound-assisted compression of powders have prevented optimizing the processing steps for industrial pharmacy utilization. Although attempts have been made to explain some of the phenomena involved, the physical mechanisms in the process are still not fully understood.

Frederic (1965) (45) suggested that powders flow more readily under ultrasonic vibration because the tendency for particles to pack down and become locked together at an early stage is minimised by the jostling they receive. During powder compaction, based on the superposition of high power ultrasound, two different compacting phenomena occur. First, the motion of material relative to the die may take place, resulting in the reduction of friction between the material and the die wall. Second, the motion of individual powder particles relative to one another may occur, reducing the interparticulate friction, aid repacking and breaking up any prematurely formed contacts between the particles (38,44).

It has been suggested that the ultrasound-assisted compression process involved a form of thermal fusion and was best suited to those materials with a high modulus of elasticity and a low melting point (34,46–47).

Our studies, at Liverpool John Moores University (48) confirmed the idea of thermal fusion of particles during ultrasound-assisted compression (46–47). Figure 3 shows scanning electron micrographs of upper surfaces of paracetamol tablets containing 10 %w/w of polyvinylpyrrolidone (PVP, Polyplasdone, ISP, UK), prepared with ultrasound applied during compression at an applied pressure of 32 MPa.

The appearance of sinter-bridges (formed due to fusion bonding of partially melted surfaces) between particles are clearly seen on the micrographs (Fig. 3) (48).

Figure 4 shows the micrographs of paracetamol tablets containing 5 %w/w PVP, prepared by ultrasound-assisted compression (48), confirming the claim of Rodriguez *et al.* (1997) (46) that in some cases ultrasound causes material sintering which leads to a progressive transformation of open into closed pores within the tablet.

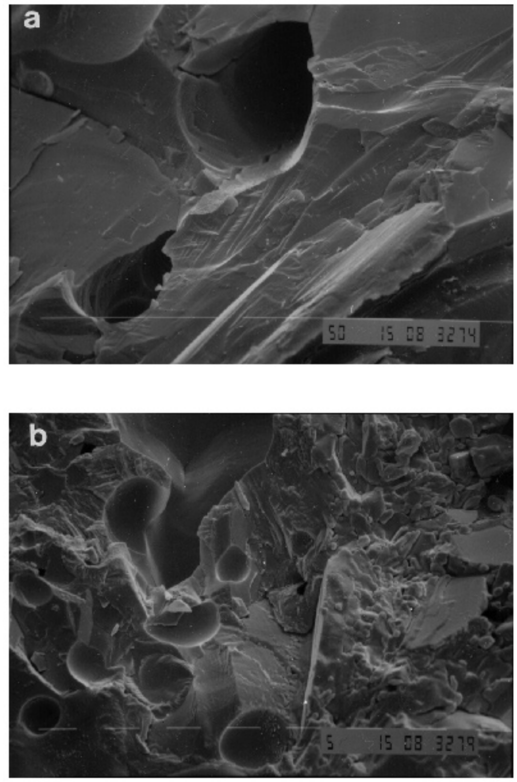

Fig. 4. Scanning electron micrographs of the fractured surfaces of paracetamol tablets containing 5 %w/w of PVP, compressed at 32 MPa with ultrasound. Magnification: a) X500; b) X1000.

APPLICATIONS OF ULTRASOUND IN PHARMACEUTICAL TABLETING

To Aid the Direct Compression Method

Although granulation is commonly carried out prior to compression of powders, the preferred method of tablet manufacture is direct compression for reasons such as simplicity, fast processing, lower costs, and increased stability of drugs (3,49).

However, direct compression of a high dose drug, such as paracetamol, which has poor compressibility and flow properties, is not possible. This is because filler-binders have a limited dilution potential (50), and tablet size and weight are limited; and thus, soft or capping tablets are produced (51–53). The use of ultrasound has the potential to eliminate those limitations and allow direct compression technique to be used even in those cases where conventional compaction fails. For instance, ultrasound-assisted compaction has been used to produce tablets with high anhydrous theophylline content formulations, which are unsuitable for direct compression (21).

To Improve Powder Flow, Tablet Density, and Uniformity

Ultrasound application during tableting can improve powder flow, tablet density (47), and uniformity due to powder "jarring and vibrating" which causes a reduction in the internal friction between the powder particles.

The increase in the apparent density (dρ) of the compacts produced under-ultrasound assisted compression has been expressed as a function (f) of (54):

$$d\rho = f(k;P_a/P_c) \qquad (1)$$

Where k is a constant depending on the pressed material, die shape, tablet shape and size, and work conditions, including the ultrasonic parameters; P_a is the acoustical pressure (i.e., ultrasound amplitude); P_c is the compression pressure applied to the material. The increase in the compact density has been related to particle rearrangement simultaneously influenced by pressing power and ultrasonic oscillations, and higher removal of air from the particle surface and pores in the compact (54).

To Improve Tablet Mechanical Strength

Coherent tablets can be prepared by ultrasound-assisted compression at lower pressures as compared to conventional tableting, exhibiting greater crushing strength and less friability (55). These improved properties of the tablets have been related to a temperature rise within the compact caused by ultrasound. In our studies (48) it was found that during tableting of ibuprofen using 32 MPa compression force and application of 1, 2, or 5 seconds ultrasound (amplitude 7 μm), the overall temperature of the tablet was increased by about 19, 30, or 36°C, respectively. Increased temperature within the tablet during conventional compression, increases the extent of plasticity and stress relaxation, while elasticity decreases resulting in an increase in tablet tensile strength (56). This may also apply to ultrasound-assisted compression, where ultrasound raises the temperature within the compact allowing plastic deformation and stress relaxation to occur, and also to increasing particle-particle contact, resulting in stronger tablets. In addition, fusion bonding might contribute to increased mechanical strength of the tablets. Local temperatures achieved during ultrasound-assisted compression facilitate interparticular bonding by asperity melting leading to the production of stronger tablets (Fig. 3).

Application of ultrasound during compression of paracetamol and ibuprofen significantly increased the compressibility of the materials leading to higher crushing strength of the tablets (48). The crushing strength of tablets significantly increased as the duration of the ultrasound application increased (48).

To Avoid Tablet Capping and Lamination

Capping is a defect in which the top or upper segment of the tablet is cracked around the edge or separated as a cap. In the compression cycle, as the punch is removed, the axial pressure is relieved but the tablet is then subjected to a radial pressure exerted by the reaction of the die wall. With substances exhibiting a weak particle-particle bonding, the radial stress may be relieved by the elastic recovery of the particles resulting in partial separation of the bonding surfaces. However, with a strong particle-particle bond, elastic recovery in the axial direction may cause capping (57). When the tablet is ejected from the die, radial expansion takes place and further faults may arise (58). The punches and dies have been claimed to contribute towards trapping the air inside the compact during a rapid compression cycle leading to capping (59). This air is compressed within the compact, as the punches move together and apply pressure, and then expands when the compression pressure is released causing capping. Lamination is caused by the same factors as capping but by exaggerated conditions at high speed. It differs from capping in that tablets split or crack on the sides causing the tablet, when ejected, to come apart or separate in layers.

Ultrasound application during powder compression can be a remedy for capping and lamination of tablets containing high-dose drugs, such as ibuprofen and paracetamol. Usually, during conventional compression, too much elastic energy is stored under compression, and then during decompression the elastic recovery breaks most of the interparticulate bonds, leading to capping (60). However, tablets compacted with the aid of ultrasound vibration might exhibit less elastic recovery due to particle dimensional stability, as they would attain their most stable orientation in the die.

It has been suggested (38,44) the application of ultrasound during compaction improves particle rearrangement of the powder bed (to a more stable orientation), leading to a greater area of contact for a given pressure and consequently, a greater degree of bonding. In addition, ultrasound can cause localized melting at the interparticle contact points resulting in the development of strong solid bridges between particles, as discussed earlier. Thus, during recovery, the stored elastic energy could be inadequate to separate extensive areas of contact with strong bonding, and as a result no capping would occur. Moreover, the trapped air in the powder can escape more readily during ultrasonic vibration.

Use of Ultrasound for Slow-Release Tablets

In recent years there has been a large increase in the development and use of sustained-release tablets which are designed to slowly release the drug, after ingestion. A tablet produced by ultrasound-assisted compression may receive increasing attention as an effective means of producing controlled drug release.

Although sustained-release tablets have many clinical advantages, they are very costly per unit dose. In addition, the physical size of the dosage form may present problems. Some patients do experience difficulty in swallowing a 600–650 mg sustained-release tablet and it is often difficult to formulate the tablets with lower weight. The use of ultrasound-assisted powder compression technique might be able to bring the cost (21) and tablet weight (61) down.

Some sustained-release formulations often require several ingredients and complex manufacturing processes such as wet granulation and film-coating procedures. In these cases the drug and the excipients are exposed to water and heat. Attempts have been made to resolve these problems by employing ultrasonic energy. Saettone *et al.* (1996) (61) and Rodriguez *et al.* (1997) (46) demonstrated the possibility of sustained-release matrix formulations by applying high-energy ultrasound during dry compression of simple mixtures containing drug and carrier.

Rodriguez *et al.* (46,55) described an ultrasound-assisted pharmaceutical tableting machine which was used for the compression of formulations containing Eudragit® RL and theophylline. Eudragit® RL was used for its thermoplastic properties and a low glass transition temperature, so that it could be softened with low energy. The powder mixtures were subjected to ultrasonic vibrations at a frequency of between 20 and 40 kHz. Compression pressures used did not exceed 3–6 MPa. It was found that the tablets prepared by ultrasound-assisted compression were harder (>20 Kg) and less friable than when they were conventionally compressed. *In vitro* dissolution studies showed that compacts produced with the aid of ultrasound had a prolonged drug release, about 50% longer than that of conventionally manufactured tablets. Moreover, the *in vitro* release rate of theophylline was a function of the ultrasound energy (55).

In another study, Saettone *et al.* (1996) (61) reported the sustained-release matrix production of theophylline using Eudragit® RL and Eudragit® RS by ultrasound-assisted compression. Slower release rates were observed for the matrices prepared with the aid of ultrasound compared to the corresponding conventionally compressed matrices. It was also found that the release rates appeared to increase with increasing theophylline content of the formulations (61). Therefore, it was suggested that ultrasound application induced melting of the acrylic polymers (*Eudragit® RL* and *Eudragit® RS*) which coated the theophylline particles. This may also promote polymer-drug interactions which leads to slower drug release from the matrices. It was also found that while standard compression of mixtures containing over 50%w/w theophylline was unsuccessful, satisfactory matrices could be obtained by ultrasound-assisted compression (61).

Based on these preliminary studies, it is possible to achieve acceptable slow-release of different drugs using mechanical or electromechanical vibrations of frequency between 1 kHz and 2 MHz to polymers or copolymers, such as cellulose and its derivatives, polyamides, acrylic polymers, polyesters, polyvinylpyrrolidone, starch and polyethylene glycols (21). Whereas by selecting excipients, such as solid sugars and cyclodextrins, a much more rapid drug release can be achieved.

CURRENT LIMITATIONS OF PHARMACEUTICAL ULTRASOUND-ASSISTED COMPRESSION

Material Suitability

When contemplating ultrasound-assisted compression of pharmaceutical powders, a few basic parameters must be studied. Most important is the suitability of the material or a mixture of materials for the technique. It must be emphasized that ultrasound-assisted compression of pharmaceutical powders is not a method which will make perfect tablets from any formulation without any problems or effort. Physical properties of the materials such as melting point, ability to undergo plastic deformation, particle size, and particle shape might affect the results of ultrasound-assisted compression.

It may be expected that ultrasound application would be beneficial for compression of materials which are known to consolidate mainly by plastic flow. Most of the published papers on the subject of ultrasound-assisted powder compression stress the importance of the presence of sufficient amount of at least one thermoplastic material in the formulation. This material when treated with ultrasound would allow the formation of a framework that would hold the rest of the formulation together (20–21,46).

Adverse Effects of Ultrasound on Tablet Disintegration and Dissolution

It is essential that after ingestion by the patient, the tablet rapidly breaks up (except when it is not intended to do so) into its constituent particles (disintegrates) and the drug is released and dissolved in the gastrointestinal fluid.

Ultrasound application during compression might adversely affect tablet disintegration and drug dissolution the extent of which depends on the formulation and ultrasound parameters utilised (48). This may be attributed to a modification in the rate of water penetration to the tablet due to the possible changes in tablet porosity and interparticulate bonding. Ultrasound can cause localized melting at the interparticle contact points resulting in the development of strong solid sinter-bridges between particles (48,62) which may be strong leading to slow disintegration and dissolution rates (63).

Drug Stability

Ultrasound can cause temperature increase within the powder bed due to ultrasonic energy dissipating as heat (55) and depending on the drug and ultrasonic parameters this might possibly lead to unwanted changes in physical or chemical characteristics of the drugs. However, the majority of the published papers on the subject of ultrasound-assisted pharmaceutical powder compression claimed that under properly controlled process conditions drug degradation did not occur (21,47,55). Rodriguez *et al.* (55) reported that no drug (theophylline) or excipient (*Eudragit® RL*) degradation occurred in the ultrasound energy range used during their compression.

Equipment Considerations

It is most likely that a significant part of the temperature increase generated by ultrasonic vibrations can dissipate to the die due to the relatively high coefficient of thermal conductivity of metal as compared to the conductivity coefficients of most materials made into tablets. Therefore, dies and punches used during ultrasound-assisted compression might have shorter life as compared to those used for conventional tableting. Besides the equipment which utilizes ultrasound should be properly tuned and regularly checked in order to prevent a possible damage to the transducer and to avoid excessive energy losses.

Safety

One of the reasons for ultrasound to be used in preference to audible sound in many applications is the fact that it is silent. High-intensity applications can often be carried out more efficiently at audible frequencies, but the resulting noise may be intolerable and possibly cause injury (12). However, even in a case of ultrasound, it is essential to consider operators' safety and therefore examine factors such as the frequency and intensity of the ultrasound generated, and the dose received by the operator.

The frequency is only indirectly important as the attenuation of an airborne ultrasound from a piece of ultrasonic equipment is proportional to the square of the frequency, i.e., the higher the frequency, the greater the attenuation, and it becomes less dangerous to the operator.

At high intensity, there is more energy available for potential harm to the operator (64). In the application of ultrasound to industrial processes the intensities used are generally higher than in control or diagnostic applications and in research work. Thus, there is more energy available as a potential source of harm to operators. In addition, the ultrasonic frequencies that are used are generally fairly low, in the range of 20–40 kHz. However, although the main frequency being used is above the human threshold frequency of hearing, it is quite probable that some audible sound may be generated, which can represent a possible danger to the operator. Therefore, the industrial use of ultrasound (high intensity and fairly low frequency) as a form of energy should not automatically be regarded as free of hazard but should be examined rather carefully.

In environmental acoustics, instead of speaking of the intensity (I) of a sound wave, it is much more common to speak in terms of sound level (β), which is defined as (13):

$$\beta = (10 \text{ dB}) \log I/I_0 \qquad (2)$$

Where dB is decibel, the unit of sound level. I_0 is a standard

Table 1. Summary of the Advantages and Limitations of Ultrasound-Assisted Compression of Pharmaceutical Powders

Advantages	Limitations
Improved powder flow	Possible potential for material decomposition
Improved tablet density and uniformity	Additional cost
Lower compression force	Unclear safety considerations
Higher tablet crushing strength	Lack of understanding of the mechanisms involved
Wider use of the direct compression method	
Reduced occurrence of tablet defects such as capping and lamination	

reference intensity (= 10^{-12} W/m^2), chosen because it is near the lower limit of the human range of hearing.

A recommended limit of 100–110 dB for industrial exposure is well below the levels at which any physiological effects of the ultrasound will occur (65). Therefore, such processes involving exposure up to that limit can be considered safe.

The subjective effects, such as fatigue, headaches, nausea, and tinnitus are thought to be due to high-frequency audible sound emitted or generated by the ultrasonic equipment, rather than to ultrasound itself (66). Thus for very low ultrasonic frequencies, which may be audible to some operators of high-intensity ultrasonic equipment, the recommended limit is 75 dB (66–67). Additionally, in order to attenuate the noise sufficiently to reduce the unpleasant subjective effects, sealed enclosures around ultrasonic equipment can be constructed.

CONCLUSIONS

The application of ultrasound during tableting and more specifically during the compression phase has major advantages (Table 1) and may provide a means of overcoming common problems in the large manufacture of tablets in the industry. However, there is a need for further research to understand the mechanisms involved during ultrasound-assisted compression of pharmaceutical powders. In addition, there is a need to study and evaluate the current and novel facilities and equipment for generation and application of ultrasound suitable for pharmaceutical materials with a view to comply with the manufacturing conditions and standards of medicinal products. We hope that this article initiates some thoughts in not only the usefulness of the method but also in the necessity of some fundamental research in the area.

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