APPLICATION OF ULTRASOUND-ASSISTED COMPRESSION IN PHARMACEUTICAL TECHNOLOGY. DESIGN AND OPTIMIZATION OF ORAL SUSTAINED-RELEASE DOSAGE FORMS

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Abstract

Ultrasound-assisted compression (USAC) is a technology combining a conventional compression process and US irradiation. These mechanical and thermal effects lead to heating, melting and sintering of materials. This article reviews the principles of ultrasound-assisted compression and its main applications in pharmaceutical technology. Physical properties of the materials and process parameters such as time, energy and inter-punch distances should be carefully controlled to guarantee reproducibility and a complete transition of the material. The application of ultrasounds during compression improves the mechanical strength of tablets, a clear advantage for formulations with high-doses of poor compressible drugs. Ultrasounds have also demonstrated its usefulness as a technique to prepare solid dispersions, enhancing the bioavailability of poorly soluble drugs. The formulation of sustained-release oral dosage forms has also benefit from the application of USAC, as a better control of drug release with a minor quantity of excipient could be obtained. The continuum percolation model provides a physical basis to explain the important decrease in the excipient percolation threshold using this technology. This model together with the quantification of the Excipient Efficiency parameter, are valuable tools to understand the drug release properties from sustained-release systems.

Keywords: Ultrasound-assisted compression; Tableting; Solid dispersion; Controlled release; Percolation threshold; Excipient Efficiency

1. Introduction

Hot-processing techniques (hot-melt extrusion -HME-, injection-molding -IM-, three-dimensional printing by fused deposition modelling -FDM-, ultrasound-assisted compression-USAC-) have emerged as new processing technologies for the development of solid dosage forms and they are showing promising results in manufacture of immediate and controlled release systems.

Ultrasound (US) energy has been used for several years in metallurgy, plastics and ceramics industries for joining dissimilar materials such as metals and polymers [1,2]. The automotive industry has used it regularly since the 1980s. Recent applications in the food field includes fine-particle removal from emulsions, agglomeration and defoaming [3].

The first applications of ultrasounds to the pharmaceutical field date from two patents in 1993 and 1994 [4,5]. Gueret [4] 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 polymer in the formulation allowed the formation of a framework that held the non-thermoplastic powders together. Motta [5] used powder mixtures of an active ingredient from 30 to 75% w/w and suitable excipients in the range from 70 to 25% w/w to obtain pharmaceutical forms applying ultrasound and mechanical compression (avoiding granulation or extrusion). The active ingredient could be released in a delayed or rapid but controlled manner based upon the choice of the excipients.

Since then, different papers [6–11] have dealt with the application of ultrasounds in pharmaceutical technology: compression of active pharmaceutical ingredients, formulation of solid dispersions to enhance the bioavailability of poorly soluble drugs and formulation of sustained release dosage forms. Nevertheless, this technique has not been widely used despite the promising results obtained. The complex phenomena involved in the process as well as the absence of a clear knowledge of the effect of the application of US energy on the final properties of the dosage form could be some of the reasons of its limited use.

The objective of this study was to review the literature concerning the application of ultrasound-assisted compression in pharmaceutical technology. Attention will be focused on the possibilities offered by this technique in the formulation of sustained release dosage forms. Moreover, the paper deals with the usefulness of the percolation theory to predict the technological and biopharmaceutical properties of matrix systems developed by USAC. This

model, together with the quantification of the Excipient Efficiency parameter, could serve as valuable tools for optimizing the design of formulations by this technique.

2. Principles of ultrasound-assisted compression technique (USAC)

Ultrasound energy refers to mechanical waves above the audible frequencies; normally frequency waves equal or higher than 20 kHz. Ultrasonic waves are of the same nature as sound waves and their propagation and absorption in various media are governed by the laws that apply to sound transmission. Even in the presence of obstacles, they are able to travel along different materials [12].

As a wave propagates through a medium, its amplitude decreases or attenuates. There are several causes of this attenuation, such as spreading of the wave front, conversion of the acoustical energy to heat and scattering from irregular surfaces [12]. The rate of propagation depends upon the type of wave, the elastic properties of the medium, the density of the medium, and, in some cases, the frequency and amplitude. The propagation speed of ultrasounds in a specific medium may be lower or higher than in vacuum.

Ultrasonic applications can be classified as being either low or high intensity. At low intensities, ultrasound is used to investigate structural properties of materials including living tissues [13]. In this case, the material under study does not suffer any permanent change in its structural and chemical properties. At high intensities, ultrasound is generally used for changing the properties of the material, being the changes often permanent. In terms of pharmaceutical powder compression, high-intensity ultrasound is used [14].

High-power ultrasound presents, in general, nonlinear interactions. Such interactions may involve shock waves and harmonic generation (inducing cavitation phenomena) and a wide range of other phenomena that are thermal, mechanical and chemical in nature [12,14]:

- Thermal effects: As ultrasound progresses through a medium, energy is lost in the form of heat mainly due to reflections. The amplitude of ultrasonic vibration is directly proportional to the amount of energy converted to heat.
- Mechanical effects: Ultrasound produces agitation and random motion of the particles in the material, inducing its compaction. Stresses developed in an ultrasonic field can cause ruptures in the materials and severe erosion of their surfaces.
- Chemical effects: The primary mechanisms of enhanced chemical reactions under the influence of high-intensity ultrasound are cavitation and intimate mixing of reactive and catalytic components. Nevertheless some chemically related effects of ultrasonic energy are due to absorption of heat, especially oxidation reactions. Ultrasound has

been reported to promote polymerisation or de-polymerisation depending upon the nature of the molecules being treated.

Thermal and mechanical effects are involved in the production of tablets by ultrasound-assisted compression. Besides these effects on solids, US also acts on liquids or melt mixtures, causing cavitation and an extreme molecular motion that divide a drop of liquid material into a number of microdrops with a very narrow range of sizes. This physical principle could be employed to prepare multiparticulate drug delivery systems [8].

Ultrasound-assisted compression equipment contains the following basic components:

- US generator: 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. In the pharmaceutical field 20 kHz is used. Outputs may vary from 50 watts to several kilowatts as required.
- Transducer: Converts the high-frequency electrical output of the generator into high-frequency mechanical vibrations. Usually piezoelectric transducers are used (mainly made with special ceramic materials).
- Acoustic coupler (sonotrode): Focuses, amplifies and transmits the mechanical vibrations from the transducer to the powder in the die.

Time, energy and amplitude of the US-waves are carefully controlled in order to achieve the transition of the material and manufacture the tablets. Time from 4 to 10 seconds, energy from 400 to 1400 Joules and inter-punch distances below 7 mm are currently used. Distances larger than 7 mm lead to high variability of results and poor transitions of the material. Although the use of ultrasounds increases the compaction time compared with conventional direct compression, the enhanced compactibility and more homogeneous distribution between drug and excipient [15,16] obtained by USAC could overcome this drawback. Moreover, this technique reduces the quantity of material and the production time compared with contemporary hot-processing techniques such as HME [10].

Fig. 1 shows the process of the manufacture of a tablet by means of ultrasound-assisted compression. In the initial state (Fig. 1a) sample is poured into the die covered at the top and bottom by tetrafluoroethylene (Teflon®) sheets. Pressure is applied with the lower punch to achieve a precompaction of the sample (Fig. 1b) ensuring a good transmission of ultrasound energy from sonotrode to the material. Ultrasound is applied by the upper punch-sonotrode (Fig. 1c) and the movement of the powder particles increases, increasing their packaging and the friction and collisions between them. As a consequence, the temperature rises producing a glass transition to the rubbery state of those components with thermoplastic properties. This stage lasts until a preset parameter (the sonication energy, the sonication time or the final

position of the lower punch) is reached. After a cooling stage (Fig. 1d), a period to reestablish the new solid properties of the sample, the tablet is ejected (Fig. 1e). It is important to emphasize the need to use a Teflon® sheet to protect the sonotrode and the lower punch. It also serves as thermal insulator. Under well-controlled working conditions, contamination of the tablets with Teflon is unlikely, as its melting point is higher than 300 °C.

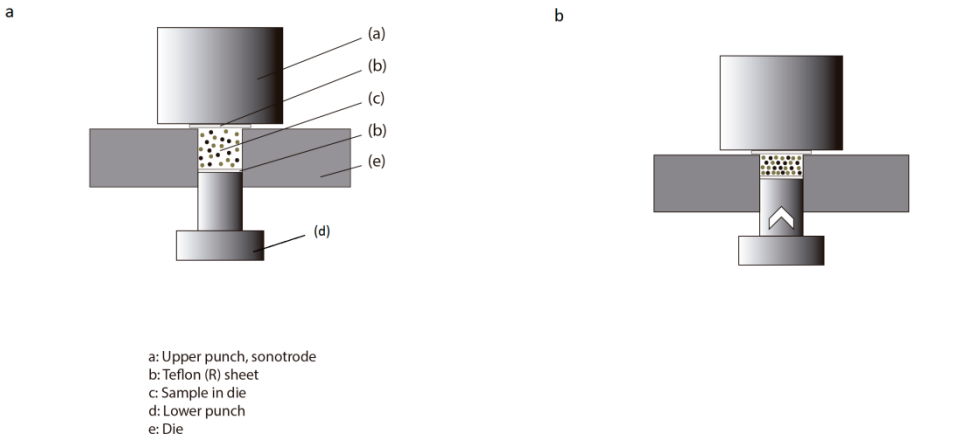

Fig. 1. Ultrasound-assisted compression process. (a) Initial stage, (b) Precompaction, (c) Compaction assisted with ultrasound irradiation, (d) Cooling stage and (e) Ejection of tablet.

In summary, in the process of ultrasonic compression, the porosity of the powder material is reduced by a conventional compaction process and the US irradiation from a generator coupled to the upper punch causes powder friction, leading to heating and sintering of materials.

Aspects such as material suitability and/or drug stability should be taken into account when applying ultrasound-assisted compression. Physical properties of the materials such as melting point, ability to undergo plastic deformation, particle size and particle shape might affect the results of this technique [17].

The particle size and shape affect the transmission of the compaction force and the characteristics of the resulting tablet [10]. The amount of material used for manufacture of the tablets is then limited by its bulk density.

As USAC process involves a form of thermal fusion, it was best suited to those materials with a high modulus of elasticity and a low melting point. In addition to the melting point, the glass transition temperature (T_g) of the polymer is a crucial factor in the heating process as the physical change of the polymer during the ultrasound compaction is predominantly affected by this parameter. The required US energy for a complete transition of the polymer increases with T_g [10].

When the thermoplastic polymer is subjected to temperatures higher than the T_g, mechanical pressure and frictional forces, the sintering of the particles can be produced causing the boundaries between them to be indistinguishable. In this way the excipient surrounds the pharmaceutical active ingredient more efficiently.

However, the temperature increase caused by ultrasounds within the powder bed might also lead to unwanted changes in physical or chemical characteristics of the drug [17]. Properly controlled process conditions should be established to avoid drug degradation. Several authors [16,18] have reported no degradation of the drug using different analytical techniques.

A good understanding of the relationship between the US compaction parameters and the material properties is thus necessary to guarantee the quality of the US-compacted product.

3. Application of ultrasounds in pharmaceutical powder compression

The preferred method of tablet manufacture is direct compression, for reasons such as simplicity, fast processing, lower costs and increased stability of drugs. However, direct

compression of a highly dosed drug, such as paracetamol, which has poor compressibility and flow properties, is not possible.

On the other hand, the compression of a powder is a complex process that is usually affected by different kinds of problems. These problems have been widely investigated and mainly concern the volume reduction and the development of strength between the particles of the powder, sufficient to keep the tablet integrity [19]. The application of ultrasound energy has shown a great ability to reduce and even avoid these problems.

Poor compactibility of pharmaceutical powders is one of the main causes of tablet defects such as friability, sticking, capping, lamination… Ultrasounds improve the characteristics of the compression process leading to optimized mechanical strength of the compacts at lower pressures as compared to conventional tableting. Ultrasounds cause a temperature rise within the tablet that increases the extent of plasticity and interparticle bonding, resulting in stronger and less porous tablets [15,17]. Levina and Rubinstein [9] prepared coherent ibuprofen tablets by ultrasound-assisted compression at pressures as low as 20-30 MPa. The breaking forces of these tablets were found to be significantly higher than the obtained for conventional compaction. The crushing strength of the tablets significantly increased as the duration of the ultrasounds application increased.

The application of ultrasounds during compaction favours particle rearrangement in the powder bed, leading to an increase in the apparent density, a larger area of contact and consequently, a higher degree of bonding. In addition, melting at the interparticle contact points results in strong solid bridges between particles. Thus, tablets exhibit less elastic recovery and are less likely to cap. Moreover, the trapped air in the powder can escape more readily during ultrasonic vibration [17,20].

4. Application of ultrasounds in preparation of solid dispersions

The development of poorly soluble drugs has increased in the last decades, leading to the need of formulations that enhance their solubility and, therefore, their absorption. Among solubility enhancement technologies, solid dispersion is one of the most useful and could be obtained by solvent, melting and/or mechanical methods. Ultrasound-assisted compression technique has been evaluated as an alternative method for bioavailability enhancement of poorly soluble drugs by means of a direct processing of the powder mixture, in the absence of organic solvents or evaporating apparatus [15].

Sancin et al. [21] reported the amorphisation of ketoprofen, a poorly water-soluble drug, by US compaction treatment. The drug appeared as a soft and dense paste (due to melting at 96 °C) and the crystallinity was recovered after few hours from the US treatment. Binary mixtures of ketoprofen with Eudragit® S100, a thermoplastic acrylic polymer soluble at pH > 7, were also compacted by USAC. DSC studies revealed a decrease in crystallinity of ketoprofen depending on the excipient/drug ratio and the US energy supplied. The presence of Eudragit® slowed down or prevented the regeneration of the drug crystallinity as the molten phase adsorbed on the surface of the excipient particles maintaining the drug in this glassy state. The authors conclude that this association could be interesting in the preparation of pH controlled dosage forms that release the drug in the physiological medium of the intestine.

A further demonstration of important physical modifications of solids compacted under US was reported by Fini et al. [8]. US-discharge during compaction reduced the crystallinity of both drug and excipient in solid dispersions containing indomethacin (a poorly water-soluble drug) and low melting excipients such as polyethyleneglycols (PEGs) of different molecular weights. Indomethacin was partially dissolved in the excipient causing an increase of the dissolution rate of the drug. The extent of a back-crystallisation, which reduces the dissolution rate, as a function of the ageing of the material, depends on the type of the selected PEG.

As a continuation of this research, physical mixtures of indomethacin with lactose-based excipients (Ludipress® and Cellactose®) were compacted with the aid of ultrasounds [22] to prepare a new generation of granules by milling of US-compacted matrices. Important modifications were observed on indomethacin physical state, being the drug spread on the excipient particle surface as a thin film, giving a lustrous appearance. No influence of ultrasounds was observed on phase transition concerning lactose. Dissolution profiles suggested an increased release of the drug from the systems treated with ultrasounds with respect to a traditional compaction.

Kalidova et al. [18] examined also the feasibility of US-assisted compression technique in preparation of solid dispersions using fenofibrate (a poorly water-soluble drug) and various polymers (Eudragit® EPO, Kollidon® VA 64, Soluplus®, HPMC 2910/5, Povacoat® MP) as carriers. The ultrasound energy was not sufficient enough to cause a complete amorphisation of the crystalline drug substance. An enhancement in dissolution behavior was achieved compared to the untreated physical mixture of drug and excipient but the dissolution profiles were similar to those obtained by adding the polymeric carrier directly to the dissolution medium. Moreover, the authors addressed the importance of monitoring the US compaction

process as the variables sonotrode to die distance and ultrasound application time were identified as crucial parameters for the reproducibility of the results. In this study the sonotrode to die distance was kept constant at 16.08 mm, so it is not surprising that the ultrasonic energy do not provide a significant effect at this distance.

Ueda et al. [10] stated that US compaction can be applied to improve the physical properties of a drug by the thermal effect and also offers the advantages of requiring only milligrams of sample and only several tens of seconds per compaction. The authors investigated in detail the relationship between the US compaction parameters and the polymer glass transition in order to establish the optimal setting conditions for preparing miscible amorphous drug-polymer dispersions. PVP90, PVP30, PVPVA, Kollicoat® IR, Kollidon® SR and Soluplus® were selected as model polymers.

5. Application of ultrasounds in the formulation of sustained-release dosage forms

US compaction appears as a promising technique for the development of sustained-release oral dosage forms. Although sustained-release tablets have many clinical advantages such as better patient compliance and lower side effects, they are very costly per unit dose. In addition, it is often difficult to formulate tablets with acceptable weight and the patients could experience difficulty in swallowing the dosage form. The use of ultrasound-assisted powder compression technique might be able to bring the cost and tablet weight down [20].

Several authors [6,7,11,23,24] have studied the use of ultrasound-assisted compression as a tool to prepare controlled release drug delivery systems in a simple way.

Saettone et al. [25] reported the production of sustained-release matrices 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 ultrasounds compared to the corresponding conventionally compressed matrices. The authors indicated that ultrasound application induced melting of the acrylic polymers that coated the theophylline particles leading to slower drug release from the matrices. The release rates appeared to increase with increasing theophylline content of the formulations.

Rodriguez et al. [6] also compacted mixtures of Eudragit® RL and theophylline by means of ultrasound-assisted compression at energies ranging between 15 and 150 J. SEM microphotographs showed a glassy matrix of amorphous excipient containing embedded islands of theophylline crystals. *In vitro* dissolution studies showed that compacts produced with the aid of ultrasounds had a prolonged drug release. These authors indicated that the *in*

vitro release rate of theophylline was a function of the ultrasound energy and could be correlated with the tablet porosity.

Our research group [7,23] proposed the Percolation Theory as a theoretical model to interpret the technological and biopharmaceutical differences between ultrasound compacted tablets and traditional tablets.

This theory, derived from Statistical Physics, supposes the existence of a regular lattice underlying the system. The most interesting concepts of this theory are the "percolating cluster" and the "percolation threshold". As a function of their relative volume ratios, the drug and/or excipient in a matrix system constitute a "percolating cluster", formed by particles of the same component that "touch" each other from one side to the other of the tablet. The drug and excipient "percolation threshold" is the concentration (v/v) above which a percolating cluster appears for the first time and usually represents a critical point of the system [26]. Close to this point, important changes can be observed in some properties of the system, for example in the release mechanism of the active agent or in the tablet structure. Several authors have estimated the percolation threshold of different pharmaceutical systems [27–29].

In order to investigate the influence of the compression process on the control of drug release, Caraballo et al. [7] prepared matrix systems from binary mixtures of KCl (a model drug) and Eudragit® RS-PM with different drug contents (10-90% w/w) by direct compression and ultrasound-assisted compression. Fig. 2 illustrates the drug release profiles for varying drug loads from both traditional and US tablets. A clear difference between the drug release profiles can be appreciated, showing the traditional tablets higher drug dissolution rates than US tablets. As expected, an increase in drug load accelerates drug release.

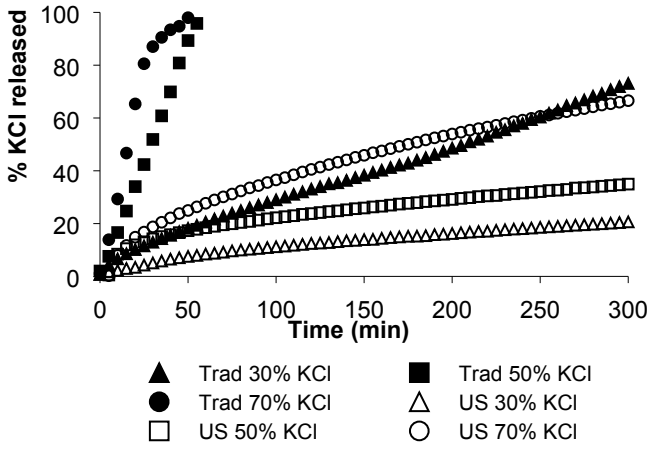

Fig. 2. Influence of KCl dose on drug release profiles from traditional tablets (Trad) and ultrasound tablets (US).

Ultrasound compaction lowered the percolation threshold of the thermoplastic excipient and this resulted in a drastic reduction (about 50%) in the amount of the thermoplastic matrix forming excipient needed to obtain a similar release rate, as well as in a better control of the drug release. Due to thermoplastic deformation and sintering, the structure of the excipient inside the US tablets does not correspond to a particulate system but to an almost continuum medium: the insoluble excipient almost surrounds the active agent particles slowing down the contact with the dissolution medium (Figure 3), therefore, there is not a true excipient particle size inside these matrices.

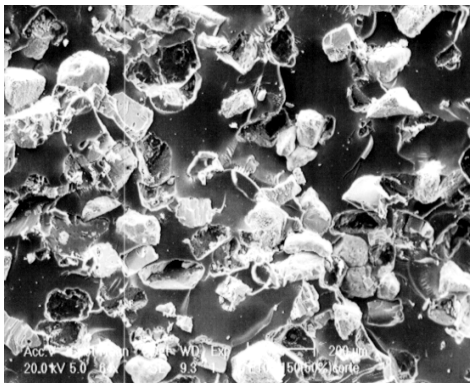

Fig. 3. SEM micrograph showing the cross section of US tablets with 50%w/w drug content. KCl (white particles) is surrounded by the excipient (shadow).

The continuum percolation model can explain the important decrease in the critical point corresponding to the excipient percolation threshold. This model dispenses with the existence of a regular lattice underlying the system; therefore, the substance is not distributed into discrete lattice sites. The continuum percolation model deals with the volume ratio of each component and a continuum distribution function. The volume ratio is expressed as a space–occupation probability to describe the behavior of the substance [30,31].

The percolation threshold of a substance in the continuum percolation model is situated at approximately 16% v/v of occupation probability (p_{cExc} = 16% v/v). The value obtained by Caraballo et al. [7] for the excipient percolation threshold (13.4% v/v < p_{cExc} < 20.2% v/v) is in agreement with this continuum percolation model.

In case of one component of the system undergoing thermoplastic deformation, the continuum percolation model can be used to predict the changes in the system with respect to a traditional pharmaceutical dosage form.

The percolation threshold for the drug in both US and traditional tablets were estimated following the method of Leuenberger and Bonny modified by Caraballo et al. [32]. The value obtained for US tablets (58.61 - 61.01% v/v) was clearly higher than the calculated for the traditional ones (26.68 - 42.19% v/v). This value for the drug threshold cannot be explained in terms of the continuum percolation model, due to the fact that the drug particles did not undergo thermoplastic deformation and therefore they did not form a continuum medium.

Following a lattice percolation model, the high percolation threshold found in the US tablets for the drug particles, could be interpreted as a consequence of the high relative particle size of the drug [33]. In this case, the thermoplastic deformation of the excipient and the formation of a continuum medium have to be interpreted as a reduction of particle size for this component that tends to occupy a minor volume and can better fill the cavities among the KCl crystals.

Millán and Caraballo [23] studied the influence of the drug particle size on the percolation threshold of the drug in ultrasound compacted tablets. Matrices containing the model drug KCl with different particle sizes and Eudragit® RSPM as a thermoplastic excipient were obtained, keeping the polymer particle size constant and using direct compression and ultrasound-assisted compression techniques. Fig. 4 shows that an increase in drug particle size resulted in a decrease in the drug release rate for traditional tablets. A different behavior was seen for US-tablets, with very similar drug release profiles, showing a diffusion release mechanism and drug release rates nearly independent of drug particle size.

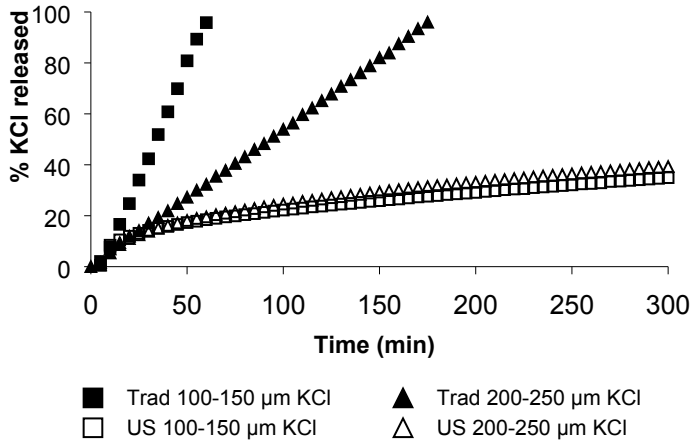

Fig. 4. Drug release profiles of traditional tablets (Trad) and ultrasound tablets (US) containing 50%(w/w) KCl and 50%(w/w) Eudragit® RSPM. The excipient particle size (100-150 µm) was kept constant and the drug particle size was different.

According to the model proposed by Aguilar-de-Leyva et al. [34] studying clozapine matrix pellets, the influence of the particle size on the drug release rate is almost negligible when the formulations are far enough from the percolation threshold. Assuming that the excipient was adopting a fluid-like distribution, coating the drug particles, the assayed formulations using coarser or finer particles are all of them clearly far away from the drug percolation threshold.

In that case, the only difference between the lots would be the magnification with which the theoretical system was observed. Therefore, the lots with larger drug particles would correspond to the system observed with higher magnification and the lots with smaller drug particles to the system observed with a lower magnification.

This situation was first described by Millán and Caraballo [23], concluding that the average drug percolation threshold, measured in these lots, would only change by the effect of the sample size, L. This variation is described by the following equation [26]:

$$p_{c\,ave} - p_c \propto L^{-1/\nu}$$

Being $p_{c\ ave}$ the average value of the percolation thresholds measured experimentally in the studied tablets, p_c the percolation threshold in the infinite theoretical system and *v* a critical exponent, which in three-dimensions equals 0.9.

As it was already mentioned, some authors attributed the effects of US-assisted compression to the reduction of the porosity experienced by the solid forms subjected to this process [6]. In order to separate the influence of the porosity from the effect of other factors, such as a change in the distribution pattern of the excipiet due to sintering and thermoplastic deformation, Caraballo [35] proposed a new parameter, the Excipient Efficiency (EE), that includes a correction of the influence of the porosity, providing an estimation of the capability of different excipients to reduce the drug release rate at similar porosity values. Two new correction factors have been recently added to EE, for the particle size and the drug solubility [24], broadening its field of application.

The Excipient Efficiency has been calculated for both traditional and ultrasound tablets. Ultrasound-assisted compression produced an increase of, approximately, 275% in the efficiency of Eudragit® RSPM to control the drug release [24]. The obtained EE values showed

that the lower porosity is not the only factor responsible for the slower release rate and additional factors as a better coating of the drug particles due to sintering or thermoplastic deformation of the excipient particles, contribute to decrease the drug release rate.

In such a way, ultrasound-assisted compression allows the manufacture of tablets that control the release of the drug with very low percentages of excipient. For example, Aguilar-de-Leyva et al. [11] developed sustained release hydrophilic matrix tablets with 750 mg of APIs and different hydrophilic excipients (Carbopol 971P, 71G and 974P, Methocel A15LV and pregelatinized starch) using a maximum percentage of excipient of 15% w/w, making possible a twice a day administration of deferiprone. This fact may suppose an important advantage for the pharmaceutical industry, as controlled release matrices with a high drug content can be prepared with a very little increase in the weight of the system.

6. Conclusions

US-assisted compression has shown in less than two decades arguments to be a competitive technology to produce almost instantaneous amorphisation of APIs, solid dispersions or high efficiency sustained release systems. Nevertheless, its development is being slow in the field of pharmaceutical technology, probably because of the resistance of pharmaceutical industry to incorporate “radically new” technologies or in the absence of an adequate background to properly apply the technology.

The calculation of the Excipient Efficiency has demonstrated that the effect of USAC of thermoplastic excipients is clearly beyond the porosity reduction. Continuum percolation provides a rational model to explain qualitatively and quantitatively this effect.

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FIGURE LEGENDS

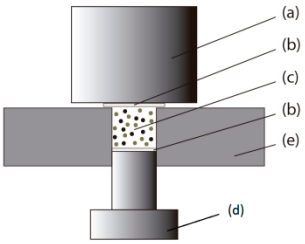
Fig. 1. Ultrasound-assisted compression process. (a) Initial stage, (b) Precompaction, (c) Compaction assisted with ultrasound irradiation, (d) Cooling stage and (e) Ejection of tablet.

Fig. 2. Influence of KCl dose on drug release profiles from traditional tablets (Trad) and ultrasound tablets (US).

Fig. 3. SEM micrograph showing the cross section of US tablets with 50%w/w drug content KCl (white particles) is surrounded by the excipient (shadow).

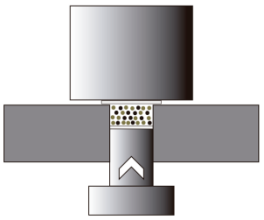
Fig.4. Drug release profiles of traditional tablets (Trad) and ultrasound tablets (US) containing 50%(w/w) KCl and 50%(w/w) Eudragit® RSPM. The excipient particle size (100-150 µm) was kept constant and the drug particle size was different.

a

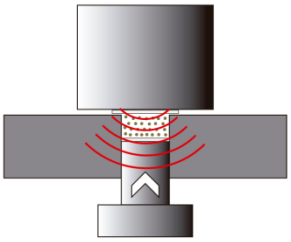


a: Upper punch, sonotrode
b: Teflon (R) sheet
c: Sample in die
d: Lower punch
e: Die

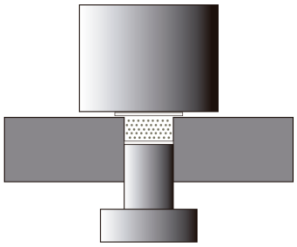
b



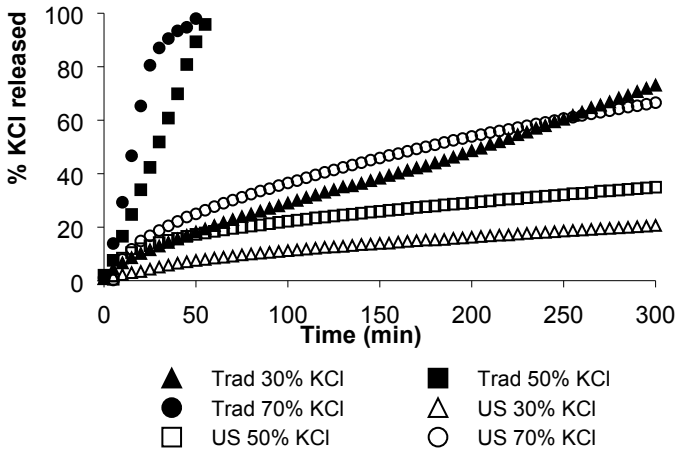
c

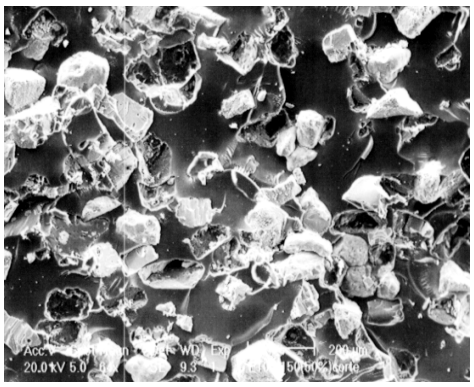


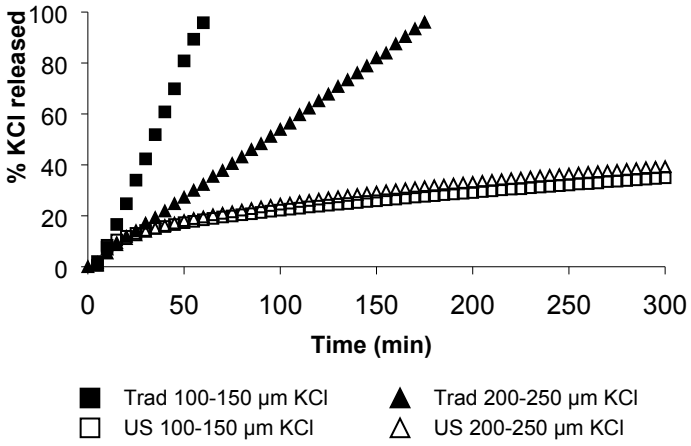
d



e


% KCl released
100
80
60
40
20
0
0
50
100
150
200
250
300
Time (min)
Trad 30% KCl
Trad 50% KCl
Trad 70% KCl
US 30% KCl
US 50% KCl
US 70% KCl


20.0kV 5.0
9.3


% KCl released
100
80
60
40
20
0
0
50
100
150
200
250
300
Time (min)
Trad 100-150 µm KCl
US 100-150 µm KCl
Trad 200-250 µm KCl
US 200-250 µm KCl