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Evaluation of theophylline tablets compacted by means of a novel ultrasound-assisted apparatus

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Abstract

A model formulation containing theophylline and Eudragit® RL was compacted, at energies ranging between 15 and 150 J, by means of a laboratory-scale, novel tabletting machine in which compaction was effected by ultrasound, rather than by mechanical energy. Comparison of the technological and physico-chemical characteristics of the resulting tablets with those of tablets obtained with a conventional tabletting machine evidenced significant differences, suggesting sintering as the main mechanism operating in ultrasound-assisted compaction. The ultrasound-compacted tablets released the drug at lower rates with respect to conventional tablets. The novel technique migh prove useful for the development of sustained-release oral dosage forms containing theophylline or other suitable drugs.

Keywords: Ultrasound; Powder compaction; Tablets; Theophylline; Eudragit® RL; Controlled release

1. Introduction

Ultrasound (US) energy has been used for several years to weld or mould plastic materials, producing widely utilized industrial items such as reinforced plastic components for the automotive industry (bumpers and dashboards), plastic packaging containers etc. (Matsuoka, 1994). The recognition that many pharmaceutical polymeric excipients and some drugs are thermoplastic or show a thermoplastic behaviour prompted the present authors to test the applicability of US energy to compaction of pharmaceutical formulations, and to investigate the properties of model tablets compacted by this technique.

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In this study, powder mixtures containing theophylline and the acrylic derivative Eudragit® RL as the thermoplastic excipient were compacted using an experimental laboratory-scale tabletting machine in which the compaction of the powder bed was predominantly effected by US, rather than by mechanical energy. The physico-chemical and technological characteristics of the resulting tablets were compared with those of tablets of identical shape, size and composition, obtained with a conventional tabletting machine.

2. Materials and methods

2.1. Materials

Theophylline (TH) (particle size distribution by Scientific Instruments Sieve: 99% smaller than 250 μm and 75% smaller than 150 μm) was purchased from Fluka Chemie A.G. (Buchs, Switzerland) and Eudragit® RL (polymer conforms to 'Ammonio Methacrylate Copolymer, Type A' USP/NF 23) was kindly supplied by Rofarma Italia (Milan, Italy). These materials were used as received. All other materials and reagents were of analytical grade.

2.2. Apparatus

US-assisted compaction was carried out using a laboratory-scale, partially hand-controlled machine (Saitec, Bologna, Italy). The apparatus (Fig. 1) compacts the material into a die (d) by means of two punches. While the lower punch (e), as in a conventional single punch tabletting machine, is active only during the expulsion of the tablet, the upper punch (c) applies a low pressure to the powder (3–7 MPa) generated by compressed air in a small cylinder and simultaneously applies US energy by vibrating at 20, 30 or 40 kHz. The US energy is generated by a piezoelectric transducer (a); its amplitude is varied by a mechanical booster (b), delivering it to the material to be compacted through the upper punch-sonotrode. Both punches are made of titanium, while the die may consist of the same material, or of stainless steel, internally coated with a thin tetrafluoroethylene (Teflon®) film to reduce the frictional and ejecting forces. The whole compaction cycle for the upper punch-sonotrode is controlled by a microprocessor (not reported in Fig. 1) via the following steps:

1. the upper punch is brought down into the filled die;
2. the US discharge starts, lasting until a preset parameter (the sonication energy, the sonication time or the final position of the upper punch) is reached. The studies described in this paper were carried out setting the sonication energy to be delivered;
3. the upper punch is then automatically raised. The microprocessor also detects and shows possible errors in the whole operational sequence.

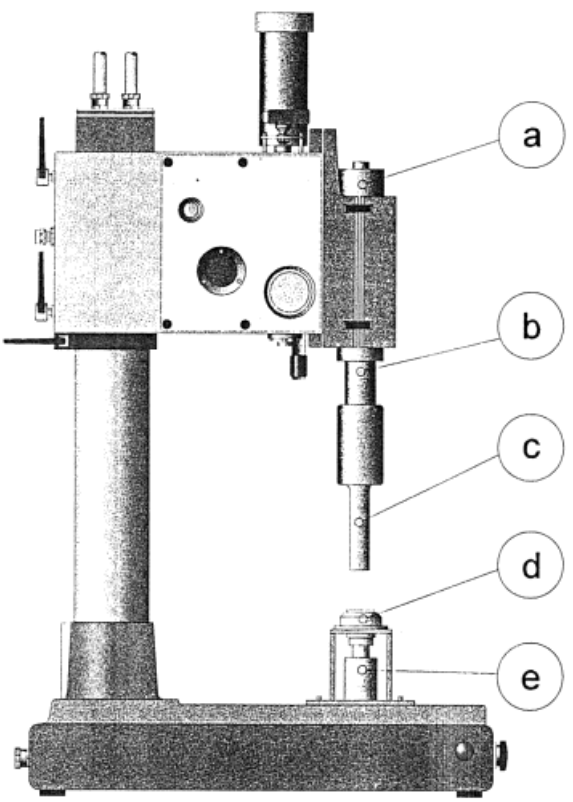

Fig. 1. Scheme of US apparatus: (a) piezoelectric transducer; (b) booster; c) upper punch-sonotrode; (d) die; (e) lower punch.

2.3. Preparation of tablets

The mixture (50 g) to be compacted with the conventional and the US-assisted tabletting machine consisted of TH (30% w/w), Eudragit® RL (68% w/w), talc and magnesium stearate (both 1% w/w), and was blended before use for 10 min at 62 rpm in a tumbling apparatus (Turbula T2C, Bachofen, Basel, Switzerland).

2.3.1. US-assisted compaction

The US tabletting machine operated at the frequency of 20 kHz, with a maximum power of 1800 W and with a booster amplifying 1.5 times the amplitude of the US wave. Different tablet batches were obtained by setting the US energy at 15, 25, 50, 75, 100 and 150 J. The sonication times ranged between 0.03 and 0.23 s, depending on the applied energy. As it can be evaluated, during the US compaction the apparatus does not always use its maximum power, because its output depends on the interactions with the material to be compacted. This behaviour is similar to the conventional compaction in which the compression force depends on the material. All tablets prepared by this technique are referred to as US tablets.

2.3.2. Conventional compaction

A single-punch tabletting machine (Korsch, Type EKO, Berlin, Germany) was used to prepare tablets by direct compression. The standard applied compression force was 50 kN. For comparison, some tablets were prepared using lower (10–40 kN) forces. All tablets obtained by this technique are referred to as C tablets.

2.4. Technological determinations

2.4.1. Temperature measurement during US compaction

The temperature vs time profile of powder samples using US compaction was monitored using the following apparatus (Wurster et al., 1995). A small thermistor (6800 Ohm at 25°C) was placed in the core of the powder inside the compaction chamber: its pins came out through small radial holes in the wall of a specially tooled, electrically insulating Teflon® die. The thermistor was connected through a linear amplifier to an oscilloscope (HP mod 54603 B) continuously displaying the output (mV). This output was converted into temperature values (°C) by means of a calibration curve, previously recorded using silicone oil.

2.4.2. Tablet porosity

The diameter, thickness and weight of both US and C tablets were 11 mm, 3.5–3.9 mm and $400 \pm 5\%$ mg, respectively. These parameters were used to calculate their apparent density (ρ_a), while the true density (ρ_t) was determined by helium pycnometry at 24°C (MultiVolume Pycnometer 1305, Micromeritics). The porosity (ϵ) of the tablets was then calculated by the equation:

$$\epsilon = (1 - \rho_a/\rho_t)$$

2.4.3. Scanning electron microscopy

The surface characteristics of the tablets were assessed by scanning electron microscopy (SEM) (Philips XL30 apparatus). The samples were preliminarily sputter-coated with gold.

2.4.4. In vitro dissolution tests

TH release from the US and C tablets was investigated using an open flow-through system, operating in sink, laminar flux conditions (USP 23). The dissolution apparatus was connected by a peristaltic pump (Gilson Minipuls 3) to a flow-through spectrometer (Unicam UV/Vis spectrometer mod. UV2), and the absorbance at 271 nm was automatically recorded. The pump operated at a rate of 12.5 ml/min and the dissolution medium was a pH 7.4 phosphate buffer at 37°C.

3. Results and discussion

The formulation used in this study was tested in a previous investigation dealing with prolonged-release, conventionally compacted monolithic matrices containing TH (Rodriguez et al., 1993). Eudragit® RL is a copolymer of acrylic/methacrylic esters containing 10% hydrophylic quaternary ammonium groups: it is a thermoplastic amorphous material with a low (55°C) glass transition temperature (T_g) (Lin et al., 1996). As a

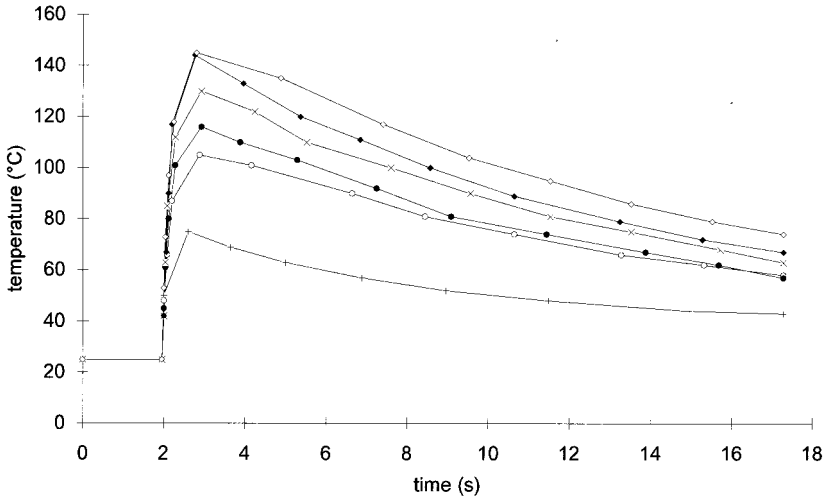

Fig. 2. Effect of US energy on temperature inside the tablets during sonication: +, 25 J; ○, 50 J; ●, 75 J; ×, 100 J; ◆, 125 J; and ◇, 150 J.

consequence it is softened by lower energies than crystalline polymers.

The temperature versus time profiles of powder mixtures submitted to compaction at different US energies are illustrated in Fig. 2. A very fast temperature rise (from room temperature to 75–150°C in a few tenths of a second) followed by a relatively fast decay was observed in all cases. The peak temperature (T_p) increased with increasing sonication energy up to 125 J: the T_p values measured at 125 and 150 J were identical. It can be assumed that the reported thermal effects are a consequence of the heat developed by thermal decay of the US energy, since the US conductivity of the pharmaceutical formulations is poor in most cases. On visual inspection, the US tablets compacted at 25 J or lower energies had a characteristic, translucent, porcelain-like aspect.

The IR and UV spectra of US and C tablets were not significantly different, even after application of very high US energies (300 J). In addition, HPLC analysis did not reveal decomposition of TH after US compaction up to 300 J. It can thus be reasonably assumed that the US method can be safely used for compaction of TH tablets.

The porosity (ϵ) of the US and C tablets was measured as a function of the US energy or of the compressional force applied. In C tablets, in agreement with literature data (Parrott, 1981), the porosity decreased with increasing compressional force, reaching a minimum value (0.32) at the highest force used (50 kN). In US tablets the porosity decreased with increasing US energy until a minimum value (0.15) was reached at 75 J. Then it increased slightly at 100 J.

These different characteristics of US and C tablets indicate a higher degree of compaction in US tablets, as also evidenced by a comparison of the true density (ρ_t) values. In C tablets this parameter remained constant as the compression force increased (Parrott, 1970), while in US tablets the ρ_t value decreased almost linearly with increasing US energy up to 75 J, then increased at 100 J. This behaviour might explain the formation, at high US energies (and high temperatures) of gaseous products remaining entrapped in the matrix. Thermogravimetric analyses (Rohm, personal communication) showed that when pure Eudragit® RL samples were heated, loss of weight was observed at 180 and 220°C. This was associated, as determined by mass spectrometry, with the development of small amounts of two main gaseous decomposition products, methylene chloride (at 180–187°C) and dimethylamino ethylene (at 220°C). The peaks corresponding to the two compounds became sharper and more distinct

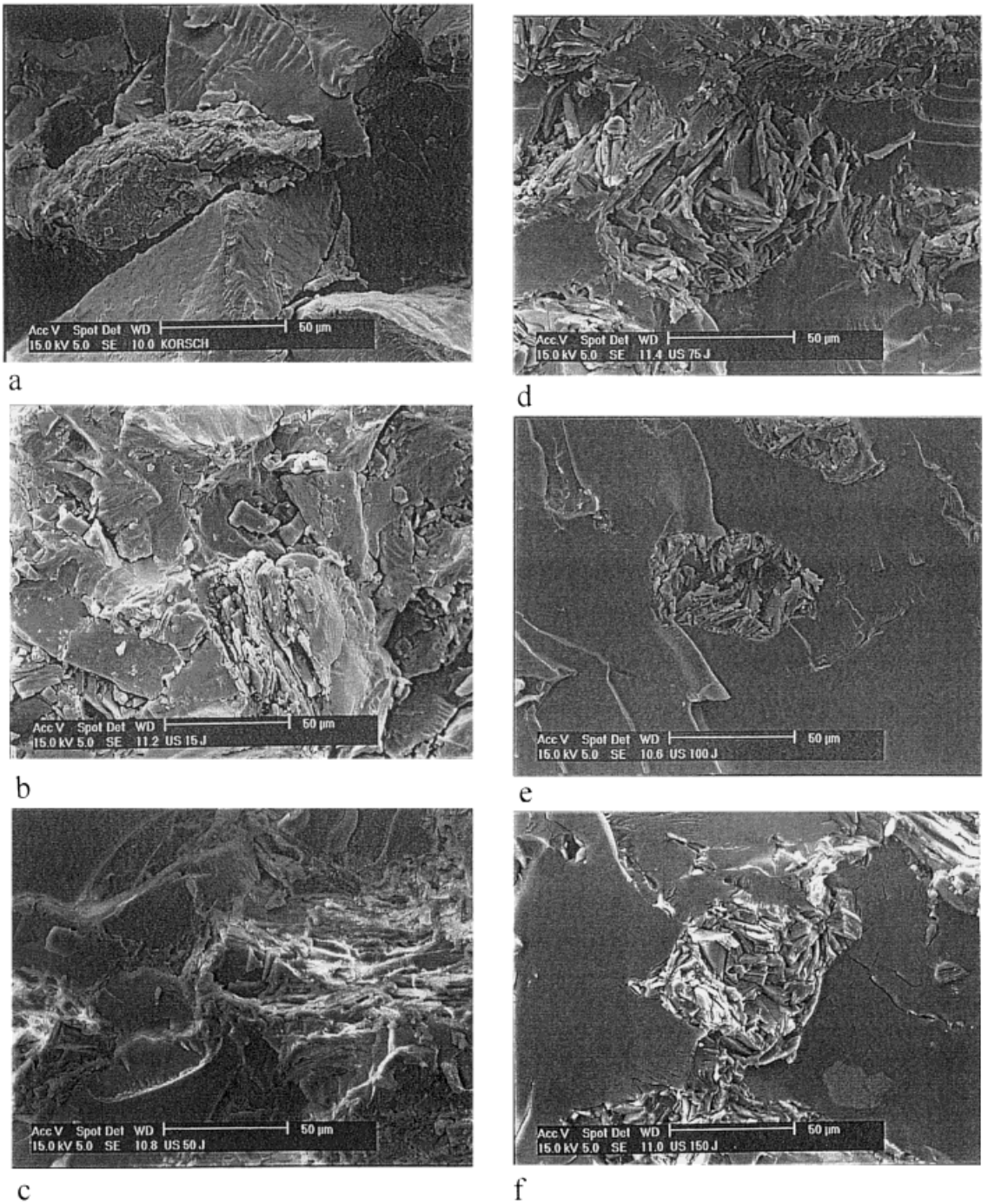

Fig. 3. SEM micrographs of: (a) C tablet; (b) US tablet (15 J); (c) US tablet (50 J); (d) US tablet (75 J); (e) US tablet (100 J); (f) US tablet (150 J).

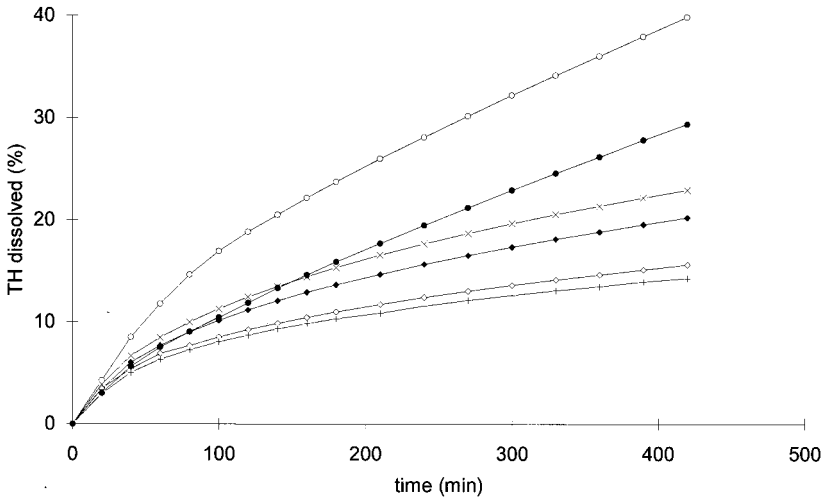

Fig. 4. Release profiles of TH from C and US tablets: ○, C tablet; ×, US 15 J; ◆, US 25 J; ◇, US 50 J; +, US 75 J; and ●, US 100 J.

with increasing temperature. Formation and entrapment of these gaseous products into tablets might explain the increased porosity, and thus the decreased density, associated with the highest US energy. It must be noted, however, that these effects were evidenced only at US energies exceeding 100 J. Thus, further research will be necessary to clarify the effect of high US energy on tablet porosity.

The microscopic surface characteristics of standard C tablets and of US tablets obtained at energies ranging between 15 and 150 J are illustrated in Fig. 3a–f. As shown in Fig. 3a, in C tablets the crystals of the active principle and of the excipient are neatly separated. According to the classic compression theory (Parrott, 1970, 1981) the particles appear welded only on their asperitics points and a continuous net of fissures forming a continuous capillary system is evident. Single particles are still evident also in US tablets compacted at 15 J (Fig. 3b), but the fissures between them are partially occluded by small crystals. The apparent density of US tablets obtained at an energy as low as 15 J was higher than that of C tablets. This may indicate that at this energy the US machine acts mainly as a multiple impact mechanical press. Conversely, US tablets compacted at 25 J show a different structure, suggestive of a glassy matrix of amorphous excipient containing embedded islands of TH crystals; fissures are no longer evident. This appearance does not vary in tablets obtained at higher US energies (Fig. 3c–f) and, according to Fig. 2, evidences the occurrence of Eudragit® RL glass transition at energies greater than 25 J, resulting from mechanical and thermal effects of ultrasounds.

The in vitro release profiles of C and US tablets are shown in Fig. 4, which illustrates the percent released TH versus time. Release was faster for C tablets than for US tablets compacted at any energy. For the latter tablets, the release rate decreased with increasing US energy up to 75 J, then increased again at 100 J. This behaviour of US tablets can be correlated with their porosity, which showed the same trend.

The fit of release data to two different release models was tested by applying a multiple regression analysis. The following equations were considered: the square-root or Higuchi equation (Higuchi, 1963):

$$(100 - M) = k_s\sqrt{t} \quad (1)$$

relative to release controlled by diffusion of the drug through the matrix; and the first-order or exponential model (Bamba et al., 1979)

Table 1
Comparison of fits for the release data using square-root and first-order equations

	Square-root			First-order		
	k_s	Sum of squared residuals	F	k_1 (10^{-4})	Sum of squared residuals (10^{-4})	F
C	2.15	0.6442	12 025.2	11.07	34.48	344.2
15 J	1.19	0.7177	3286.9	5.59	13.83	219.0
25 J	1.04	0.9559	1891.3	4.79	12.47	178.2
50 J	0.75	0.9036	1033.9	3.31	9.98	106.2
75 J	0.70	1.4397	569.5	2.87	11.87	75.5
100 J	1.59	2.9328	1435.4	7.77	3.01	1941.5

$$\ln M = -k_1 t \quad (2)$$

describing drug diffusion through a gel barrier.

The Hixson–Crowell cube root model (Hixson and Crowell, 1931), describing a release process controlled by dissolution of the drug particles:

$$(\sqrt[3]{100} - \sqrt[3]{M}) = k_c t$$

was not considered, since the tablets did not disintegrate during the dissolution tests.

In all of these models, M is the percent undissolved TH, while k_s, k_1 and k_c are the apparent release rate constant. The results of the statistical tests are reported in Table 1. The quality of fit was evaluated by residual analysis and the discrimination between the two models was effected by a F-test (cf., Bamba et al. (1979)). For C tablets and for US tablets obtained with US energy up to 75 J, the data showed a significantly better fit to the Higuchi model (the F ratio is higher than the tabulated F at 99% level of significance), while in the case of US tablets obtained at 100 J the release data fitted both models, thus indicating a more complex release mechanism.

4. Conclusions

In the conventional compaction technique a predetermined pressure (or energy) is delivered to the powder sample in a single pulse, thus producing a plastic deformation of the particles, whose magnitude is related to the applied energy. The deformation is followed by consolidation of the powder bed by cold welding. In US-assisted compaction, plastic deformation of the particles is obtained by transmitting energy at ultrasonic frequency, that is at a rate which is higher than the elastic relaxation of the material. Moreover, since pharmaceutical excipients are poor transmitters of the mechanical waves, a considerable part of the energy is degraded to heat. When one of the components in the mixture to be compacted is thermoplastic (in this case Eudragit®), the applied energy causes the transition of the polymer and the final tablets have an external glassy appearance and a higher density than traditionally compressed tablets.

The possibility of varying several parameters associated with the ultrasound discharge (sonication time, energy, frequency and amplitude of the US wave) allows us to control the technological properties of the compacted material, as well as the release characteristics of the drug.

In conclusion, the presently described US-assisted apparatus appeared suitable to compact the test formulation, and provided tablets with interesting technological properties. Their structure, as shown by the SEM pictures, was quite different from that of C tablets. The release characteristics of US and C tablets were also different, and could be satisfactorily correlated with the SEM data and the technological parameters (porosity, true and apparent density). Finally, the analytical tests on the US tablets revealed no drug or excipient degradation in the US energy range suitable for compaction (25–50 J). Thus, US compaction appears as a promising technique for the development of sustained-release oral dosage forms containing theophylline or other suitable drugs.

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