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Effect of temperature increase during the tableting of pharmaceutical materials

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ABSTRACT

Scale-up of tableting process is particularly difficult due to specific concerns related exclusively to the process itself and that cannot be determined on a smaller scale, which are the effect of compression speed and the build-up of heat due to the length of the compaction operations. In this work, it has been simulated the rise of temperature observed during the tablets manufacturing in a full production scale by means of an appropriate modification of a R&D rotary tablet machine. Four common pharmaceutical excipients, characterized by different chemical nature, consolidation behaviour and temperature sensitiveness have been analysed in terms of compaction mechanism (Heckel and energy analysis) and tabletability, in order to verify any effect of the increase of temperature.

The results showed a relevance of the temperature on mechanical tablets properties only on materials characterized by low temperature thermal transitions (melting or glass transition), while, for compounds which do not exhibit thermal events at low temperature, it becomes less important for ductile materials and irrelevant for brittle materials. Heckel analysis highlighted a noticeable increase of ductility only in those materials whose tablets mechanical properties depended on the temperature. On the other hand, energy analysis showed low sensitivity failing to identify any temperature effect on compaction materials properties.

This work showed how to simulate the process of temperature rise on a small scale and the influence of temperature on materials compaction properties. The use of a modified tableting machine, able to control the temperature and moisture levels and also capable of monitoring the punch movements, resulted in identifying the effect of temperature both on mechanical and compaction properties on materials. Thus, it represents a valuable tool in order to provide useful information at an early stage during the development of tablets formulations.

1. Introduction

Process scale-up deals with the procedures of transferring the results obtained on laboratory scale to the pilot plant and finally to production scale and it is the consequence of the scale dependency of many engineering process.

The scale-up issue can be rationally solved applying the analysis of similarities among different scales. These approaches, named dimensional analysis, are based on the recognition that a mathematical description of a physico-technological problem can be of general validity only when the process equation is dimensionally homogenous, which means that it must be valid in any system of dimensions (Zlokarnik, 2001).

Dimensional analysis has been used in the scale-up of a several pharmaceutical processes, as blending, drying, granulation, grinding, etc. and a large collection of literature in pharmaceutical process scale-up can be found (Levin, 2001). However, dimensional analysis is difficult to apply for some processes, as for example in tableting. The scale-up of compaction shows several specific concerns related exclusively to the compaction step and that cannot be determined on a smaller scale, such as the compression speed and the build-up of heat due to the length of the compaction operations (Schwartz, 2001). The speed problem can be solved using specific devices, named "compaction simulators", able to simulate the high speed compaction processes, typical of a production rotary machines, using small amount of material (Celik and Marshal, 1989;

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Michaut et al., 2010; Picker, 2000). Concerning the influence of the temperature increase on the compaction performance, at the moment there is no way to simulate such an effect on a laboratory scale.

Although the development of heat and the consequent increase of temperature during tableting is a phenomenon recognized since the 60′ (Hanus and King, 1968), and afterwards deeply investigated with several techniques and theoretical models (Bechard and Down, 1992; Buckner et al., 2010; DeCrosta et al., 2000, 2001; Kapoor and Nemat-Nasser, 1998; Ketolainen et al., 1993; Klinzing et al., 2010; Travers and Merriman, 1970; Zavaliangos et al., 2008), there have been only few studies devoted to its influence on the compaction process and on tablet properties (Rouéche et al., 2006; Van Der Voort Maarschalk et al., 1997). All these studies showed a relevance of the imposed temperature on the mechanical properties of the prepared tablets, even if only model materials were analysed. In fact, in these works, no real tableting excipient or active compound was tested, but only a new synthesized copolymer (Van Der Voort Maarschalk et al., 1997) and a generic organic powder (Rouéche et al., 2006) were considered. Moreover, none of these works was intended to simulate the increase of temperature that can be encountered during tableting on industrial scale, but they were aimed to the understanding of how the temperature affects the consolidation of a compound with specific properties.

The aim of this work is to simulate the rise of temperature observed during the tablets manufacturing in a full production scale, in order to evaluate the real effect of this parameter on tablet properties, as a function of the different materials analysed and the different pressure applied. To reach this goal, a laboratory scale rotary tablet machine, as those used in R&D study, has been modified to control the temperature and humidity of the internal environment. The analysis has been performed on four tableting excipients, characterized by different chemical nature (organic and inorganic), main consolidation behaviour (fragmentation and deformation) and temperature sensitiveness (thermal transition in a relatively low temperature range).

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Avicel PH-102 batch D7519C, FMC BioPolymer, Brussels, Belgium), dicalcium phosphate dihydrate (Emcompress batch 7031X, Penwest, Reigate, United Kingdom) supplied by Loxer (Monaco), ammonio methacrylate copolymer type B (Eudragit RS PO batch G071038159, Degussa, Darmstadt, Germany) supplied by Rofarma (Gaggiano, Italy), poly ethylene oxide 600,000 Da (Polyox WSR-205 batch D179533, Colorcon, Dartford, United Kingdom) supplied by Colorcon S.r.l. (Gallarate, Italy) and magnesium stearate (Acef, Fiorenzuola D'Arda, Italy). All the materials were used as received.

Along the text the materials name will be reported with the following abbreviation: MCC for microcrystalline cellulose, PDC for dicalcium phosphate dihydrate, EURS for ammonio methacrylate copolymer type B and PEO for poly ethylene oxide.

2.2. Thermal analysis of powders

The thermal behaviour of all the powders was analysed using a dynamic mechanical analyser (DMA 8000, Perkin-Elmer, USA), equipped with a closed furnace. All the tests were performed in bending mode, using single cantilever geometry and the proper powder pocket (Royall et al., 2005). All the materials were tested applying constant deformation amplitude (0.05 mm) and frequency (1 Hz), increasing the temperature from 25 to 150 °C at a scanning rate of 3 °C/min.

All the tests were performed in triplicate.

2.3. Tableting machine set-up

An instrumented rotary tablet machine (FA/8, Ronchi, Cinisello Balsamo, Italy) has been modified in order to control temperature and moisture inside the working area.

The temperature is controlled by a Multisetpoint Controller (DRR245, Pixsys) connected with an infrared thermometer (EL301HT-X, Calex Electronics Limited) and a heating system composed by a 400 W heater (HV 031, Stego Elektrotechnik) coupled with a fan heater (4650Z, Ebm-Papst). The thermometer was placed in a vertical support inside the machine working area, facing the die plate, while the heating system was placed in the machine roof, with the heaters and the fan in the internal and external face, respectively.

The moisture control was assembled in a similar circuit, using a controller of the same type of that used for temperature, connected with a moisture probe (EE06, Pixsys) and a vapour generator. The vapour generator was connected with the tableting machine working area using an insulated pipe passing through the aspiration line. The scheme of the temperature and moisture control apparatus is presented in Fig. 1.

Preliminary tests showed that temperature and moisture systems were able to control the temperature from ambient value up to 60 °C and the moisture up to 55%.

The tableting machine was also instrumented with load cells for the force measurement and 4 LVDT trasducers (2 for the upper punches and 2 for the lower punches) for the punches displacement recording. More details on force and displacement devices set-up and calibration procedure were previously described (Cespi et al., 2008; Palmieri et al., 2005).

Preliminary test performed without the materials at 50% UR and temperature of 25, 35 and 50 °C did not highlight any effect of the environmental conditions, inside the working area of the tableting machine, on the transducers and load cells transmission apparatus (Figure SF1 in supplementary data).

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijpharm.2013.03.014.

2.4. Tablets preparation

Flat-faced compacts of 100 mg and 6 mm of diameter were prepared for all the materials selected using a rotary tablet machine (FA/8, Ronchi, Cinisello Balsamo, Italy) instrumented as reported in the previous section.

For each material at least 20 tablets were prepared working in a continuous mode at 3 different temperatures of the die plate, 25, 35 and 50 °C, and 4 different levels of pressure, 60, 90, 140 and 200 MPa. All the runs were performed at a constant value of moisture, 50%, and at a constant production speed, 20 rpm.

In order to avoid errors in the data interpretation, due to the effect of water removal and not to that of temperature, all the materials were previously tested in terms of weight variation when stored in the environmental compaction conditions. None of them showed remarkable weight variations (maximum values was 1.8% for MCC, while all the others materials showed a maximum of 0.6%) up to 325 min (Figure SF2 in supplementary data), a time by far longer than that of powders stay inside the tableting machine feeder.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijpharm.2013.03.014.

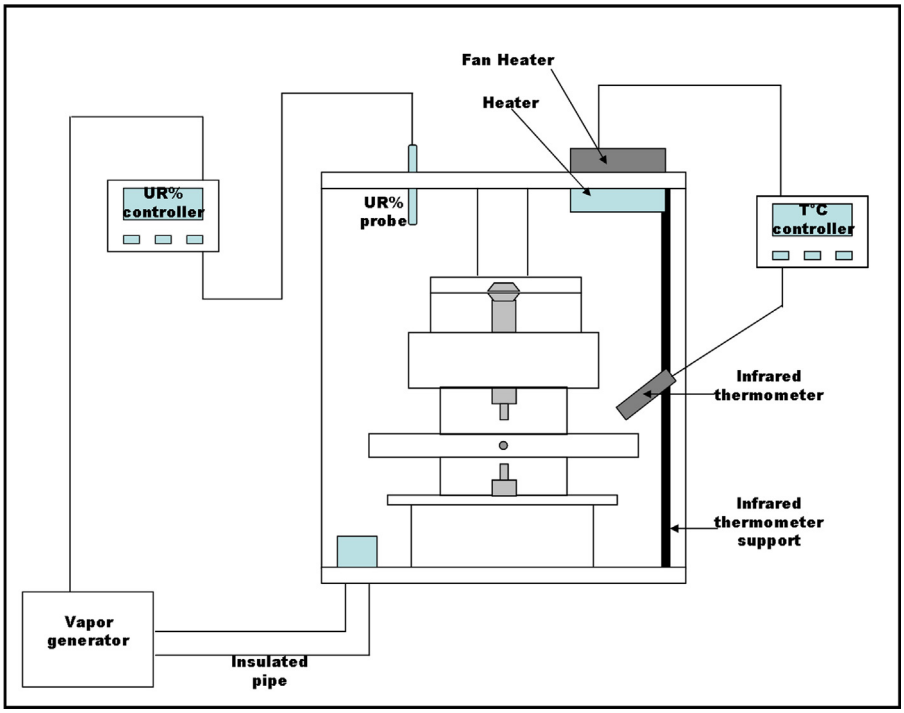

Fig. 1. Scheme of the sensors and devices used to control temperature and moisture inside the tableting machine working area.

Magnesium stearate was added to all the materials, except PEO (it is a lubricant itself), in a percentage equal to 0.5%.

2.5. Tablets and compaction data analysis

All the produced tablets were characterized in terms of weight, thickness and diameter (screw micrometre, Mitutoyo), hardness (Hardness tester TBH30, Erweka) the day after the preparation. The tensile strength (*TS*) of each tablet was determined using the relationship proposed by Fell and Newton (1970):

$$TS = \frac{2H}{\pi D t}$$

where H is the tablet hardness, t tablet thickness and D the tablet diameter.

The force and punches penetration data acquired during each single compression cycle were processed in order to perform the Heckel (Heckel, 1961a,b) and energy analysis (Nelson et al., 1955). Details of data processing for Heckel analysis were previously reported by the authors (Cespi et al., 2008; Palmieri et al., 2005), while for the energy analysis it has been followed the procedure based on the punches separation determination (Ragnarsson and Sjögren, 1983, 1985).

To evaluate the effect of temperature on tensile strength, yield pressure and energetic indexes all the data recorded at a certain pressure were subjected to analysis of variance (ANOVA) followed by the post hoc Tukey's test. Statistical analysis was performed using the software Minitab 15 considering a significance level of 0.05.

The results of statistical tests are reported on the graphs with the following symbols:

*all the data measured at the three temperature levels are statistically different;

#only one set of data at one temperature level are statistically different respect to the others.

The absence of symbols means that there are no statistical differences among all the datasets.

3. Results and discussions

3.1. Thermal analysis of powders

The materials used for this study were selected according to their chemical nature (organic or inorganic) and according to their temperature sensitiveness. Particularly, PDC is an inorganic compound while MCC, PEO and EURS are organic substances; moreover, PDC and MCC do not result to have any thermal transition in the range 20–150 °C (except the loss of moisture for MCC) (Cunha-Filho et al., 2007; Mura et al., 1995; Verma and Garg, 2005), whereas PEO melts in the range 50–75 °C (Abiad et al., 2010; Windbergs et al., 2009; Yang et al., 1996) and EURS goes through a glass transition at around 50–60 °C (Fujimori et al., 2002). All the thermal data available concerning these materials, and also those of most of the pharmaceutical materials, derive from differential scanning calorimetry (DSC) studies, a technique which measures energetic exchange between sample and ambient. DSC and its several variants (microDSC, HyperDSC, modulated DSC) represent the elective techniques to detect and analyse materials thermal transitions. However, these techniques do not allow to obtain data concerning the effect of temperature or the impact of eventual thermal transitions on materials mechanical properties, which represents valuable information if the materials have to be tableted. For these reasons, all the selected excipients were analysed using a dynamic mechanical analyser (DMA). This technique detects any thermal event capable of altering the mechanical properties of materials. The DMA results were analysed both in terms of storage modulus (E') and tangent of the phase angle ($\tan d$), as a function of temperature. The last parameter highlights the prevalence of the solid-like or liquid-like behaviour of viscoelastic materials. Moreover, it allows the easy determination of the transition temperatures since transitions appear as a peak. The storage modulus

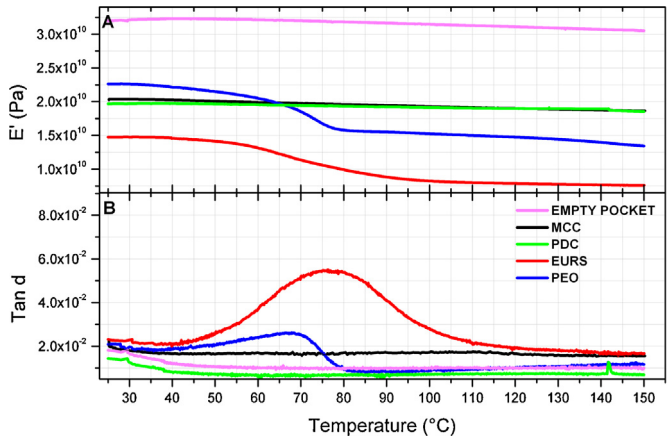

Fig. 2. Effect of the temperature on the (A) storage modulus E' and (B) tangent of phase angle tan d of all the different materials in powder forms determined during a dynamical mechanical analysis.

is instead related to the material stiffness, and a transition appears as a step indicating the increase or decrease of the material rigidity (Menard, 1999). DMA results are reported in Fig. 2. Storage modulus (Fig. 2A) and tan *d* plots (Fig. 2B) confirm the DSC results found in the literature for all the materials, showing that only PEO and EURS are characterized by a thermal transition in the analysed temperature range, at 67 and 75 °C, respectively (the values are calculated as the tan *d* peak temperature). Moreover, it can be observed that both the transitions determine a reduction of materials stiffness, more pronounced for the EURS with respect to the PEO. For the EURS, the transition observed is also wider in terms of temperature interval, beginning at around 35 °C and ending at around 100 °C. The slight reduction of E' as the temperature increases for MCC and PDC seems deriving from the aluminium pocket and not from the materials, as deducible comparing the slopes of the empty pocket (3.3×10^{10} Pa/°C) with those of the materials (2.1×10^{10} Pa/°C and 2.0×10^{10} Pa/°C for MCC and PDC, respectively)

3.2. Compaction data analysis

The four materials were selected also according to their different compaction behaviour. MCC and PEO represent two ductile materials (Celik and Marshal, 1989; Palmieri et al., 2005; Picker-Freyer, 2006; Yang et al., 1996) while PDC is a typical brittle excipient (Celik and Marshal, 1989; Doldán et al., 1995; Palmieri et al., 2005). In the literature there are no data regarding Eudragit RS compaction behaviour; however, results obtained with different type of Eudragit (Emeje et al., 2007; Tatavarti et al., 2008; Yap et al., 2008) suggest a probable predominant deforming mechanism.

The materials compaction behaviour was determined using the Heckel and energy analysis.

Heckel analysis relates the variation of powder bed porosity (ϕ) with the applied pressure (P), according with the following equation:

$$-\mathrm{Ln}\,\phi = KP + A$$

Heckel equation represents a straight line where K is the slope and A is the intercept. The reciprocal of K is called mean yield pressure (Py) and, for data acquired "at pressure" (also called "in die" method) as in this case, represents an estimation of the materials ductility (Duberg and Nyström, 1986; Fell and Newton, 1971). The linear fitting of the Heckle equation was performed in the pressure range determined initially by visual inspection and then with the method of residuals (Sonnergaard, 1999) selecting a maximum allowed residual equal to 2%. The non-linearity of Heckel plots (and sometimes the total absence of linearity) and the subsequent necessity to determine a pressure range where the plot is linear, it is frequently reported in literature (Abdel-Halim et al., 2011; Celik and Marshal, 1989; Fell and Newton, 1971; Pedersen and Kristensen, 1994; Sonnergaard, 1999; Tatavarti et al., 2008). This

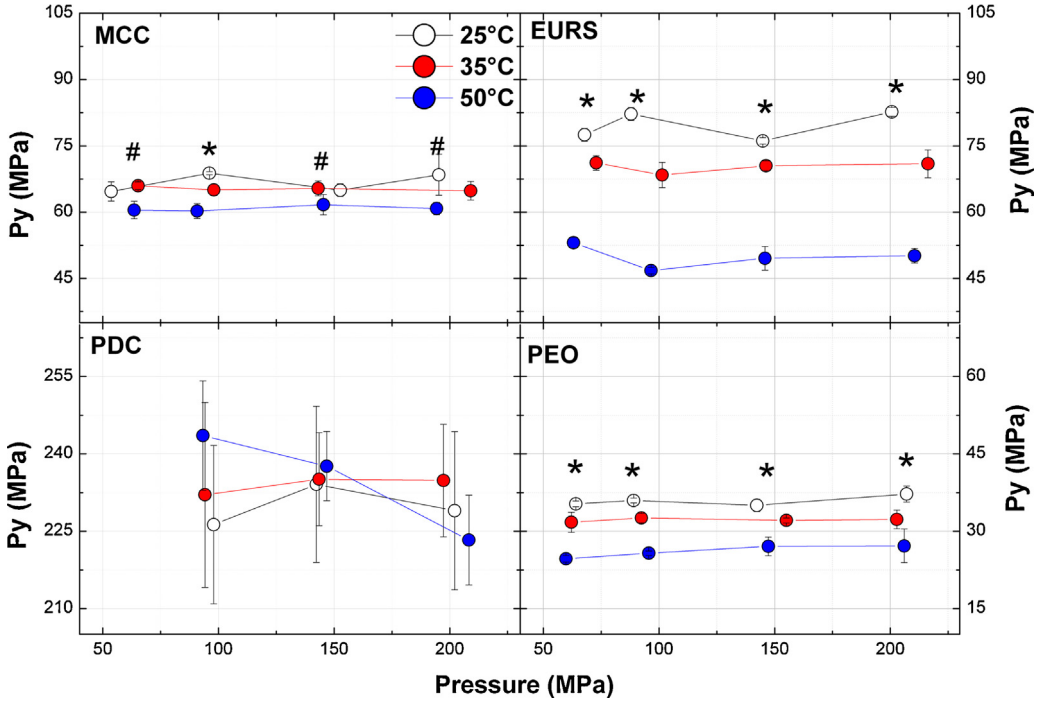

Fig. 3. Effect of the temperature and compression pressure on the yield pressure (Py) values derived from Heckel analysis for all the different materials tested. To easily compare materials with different ductility and consequently Py, the *y*-axis is set to show a Py range of 60 Mpa. Symbols * and # refer to statistical significance as reported in Section 2.5. Tablets and compaction data analysis.

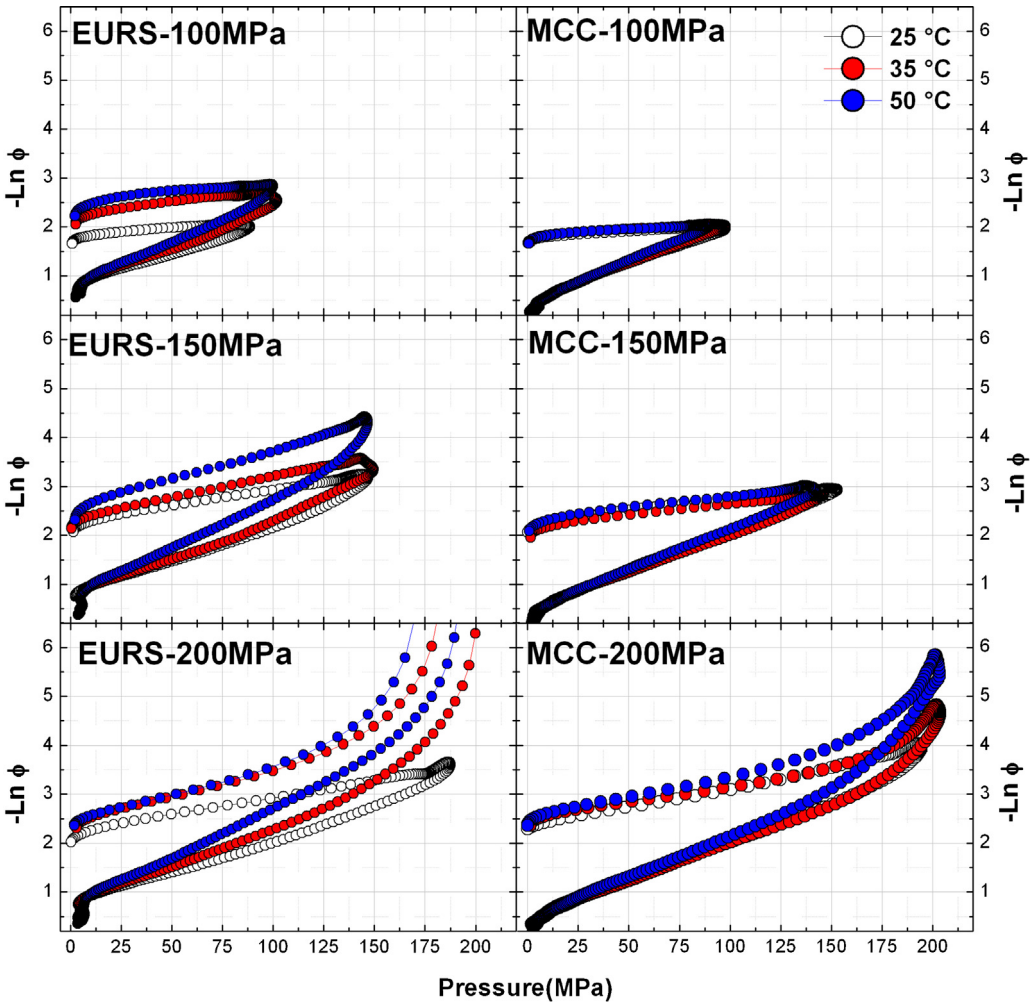

Fig. 4. Heckel plots of microcrystalline cellulose and Eudragit recorded at different pressure and temperature. The pressure value near the sample name in top the left corner represents the maximum pressure applied.

feature is commonly considered as the consequence of the presence of other densification mechanisms respect to deformation.

Yield pressure values derived from Heckel analysis are reported in Fig. 3. Py data are similar to those reported in the literature for the analysed materials (Celik and Marshal, 1989; Doldán et al., 1995; Emeje et al., 2007; Palmieri et al., 2005; Picker-Freyer, 2006; Yang et al., 1996; Yap et al., 2008) confirming that MCC, PEO and EURS are materials characterized by high ductility, on the contrary PDC got dense through other mechanisms. The results clearly show the effect of the temperature. For the materials characterized by a thermal transition at low temperature, that is PEO and EURS, the Py values are visibly dependent by the test temperature, specifically there is a reduction of Py values indicating an increase of materials ductility as the temperature increases. In the case of PDC (Py value for the pressure of 60 MPa were not measured since the traces are completely curvilinear), which is not a ductile material, the temperature does not influence the yield pressure. For MCC, the results show an intermediate situation. Indeed, there is a slightly reduction of Py values noticeable only when the temperature was at 50 °C as confirmed also from statistical tests. According to these results, it seems that the temperature plays an important role only for materials that undergo a thermally induced transition of relevance for their mechanical properties, while it becomes less important for ductile materials and irrelevant for brittle materials.

The effect of temperature it is also visible comparing Heckel plots as reported in Fig. 4 for MCC and EURS. For the EURS samples, at 200 MPa and at the temperatures of 35° and 50 °C, the $-\ln\phi$ moves towards infinite values when the pressure approaches the maximum value. This result was observed also for PEO samples at the pressure of 200 and 150 MPa for all the temperatures (data not shown), moreover also MCC seems to begin a similar process. An infinite values of $-\ln\phi$ means a negative values of porosity, that is a relative density higher than 1. Similar results are reported in the literature for acetylsalicylic acid (Pedersen and Kristensen, 1994), hydroxypropyl methylcellulose and Eudragit (Tatavarti et al., 2008). Such a phenomenon was explained by Pedersen and Kristensen (1994) in terms of variation of materials true density during compaction at high pressure. This effect was observed only for PEO and EURS, the only two materials characterized by thermal transitions at low temperature, supporting the hypothesis that the variation of material's true density during compaction is the cause of the $-\ln\phi$ infinity values. In fact, it is known that the transition from a phase to another, solid-liquid for PEO and glassy-rubbery for EURS, is associated with a change of the thermodynamic parameters such as volume, specific volume, density and heat capacity (Abdel-Halim et al., 2011).

Energy analysis is based on the measurement of the energy involved during the compaction and the decompaction phase determined through integration of the force-punch separation plots. The energy measured during the compaction phase represents the work performed by the two punches on powder bed and it is called total energy or gross energy. The energy determined during

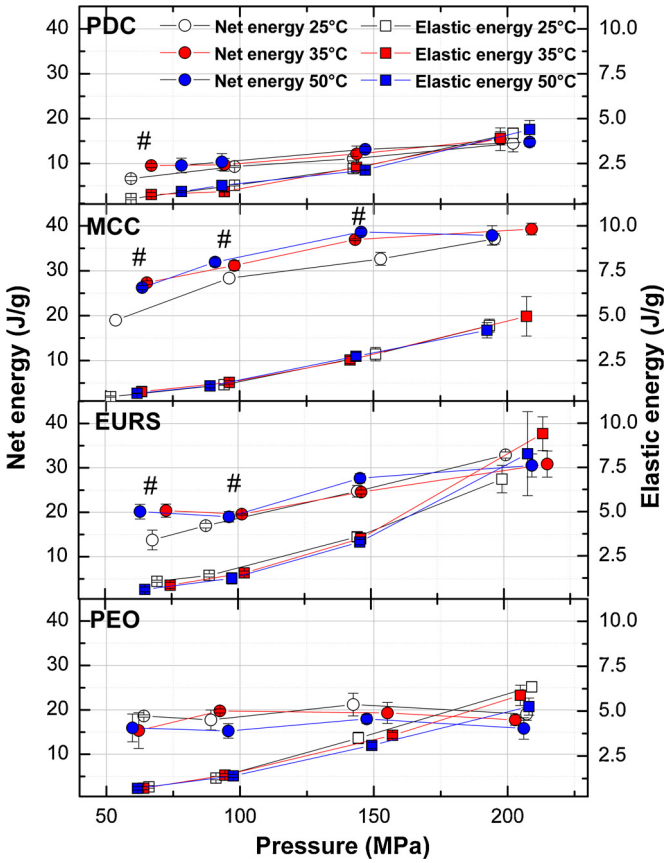

Fig. 5. Effect of the temperature and pressure on the net and elastic energy values derived from energy analysis for all the different materials tested. Symbols * and # refer to statistical significance as reported in Section 2.5. Tablets and compaction data analysis.

the decompaction phase is the work performed by the powder on the two punches and represents the material elasticity (it is called elastic energy). The difference between compaction and decompaction work is the energy effectively employed by the tableting machine to reduce the porosity of the powder bed and to form bonds between particles. This kind of energy is usually referred as net energy (de Blaey et al., 1971).

Plots of the net energy and elastic energy for all the materials at all the different experimental conditions used are reported in Fig. 5. The energetic indexes allow to easily discriminate the different materials. MCC possesses the higher net energy and PDC the lowest, while EURS and PEO are the most elastic samples. However, the energetic indexes of the four materials do not show any variation after their compression at the different tested temperatures. These results can be explained as a weak effect of the temperature on the compaction work, or as a low sensitiveness of the energetic indexes.

Tablet hardness is one of the first parameters checked during the industrial manufacturing of tablets and provides an immediate information concerning how the process is progressing. Variation of tablets hardness during the manufacturing is a typical concern to solve during the scale-up phase in order to avoid costly drawbacks during the full scale process.

Tablets hardness, normalized as tensile strength, is reported in Fig. 6. The materials show noticeable differences in terms of mechanical resistance of the produced tablets, with MCC and PEO characterized by a higher tabletability. Moreover, the tabletability data reveal also the effect of the temperature. The materials characterized by thermal transitions at low temperature, namely PEO and EURS, show an increase of tabletability as the temperature grows, while MCC and PDC are slightly or not at all affected by temperature. These results are in agreement with the Heckel analysis, which it is also able to explain the increase of hardness as an increase of material ductility as a function of temperature. Increase of ductility

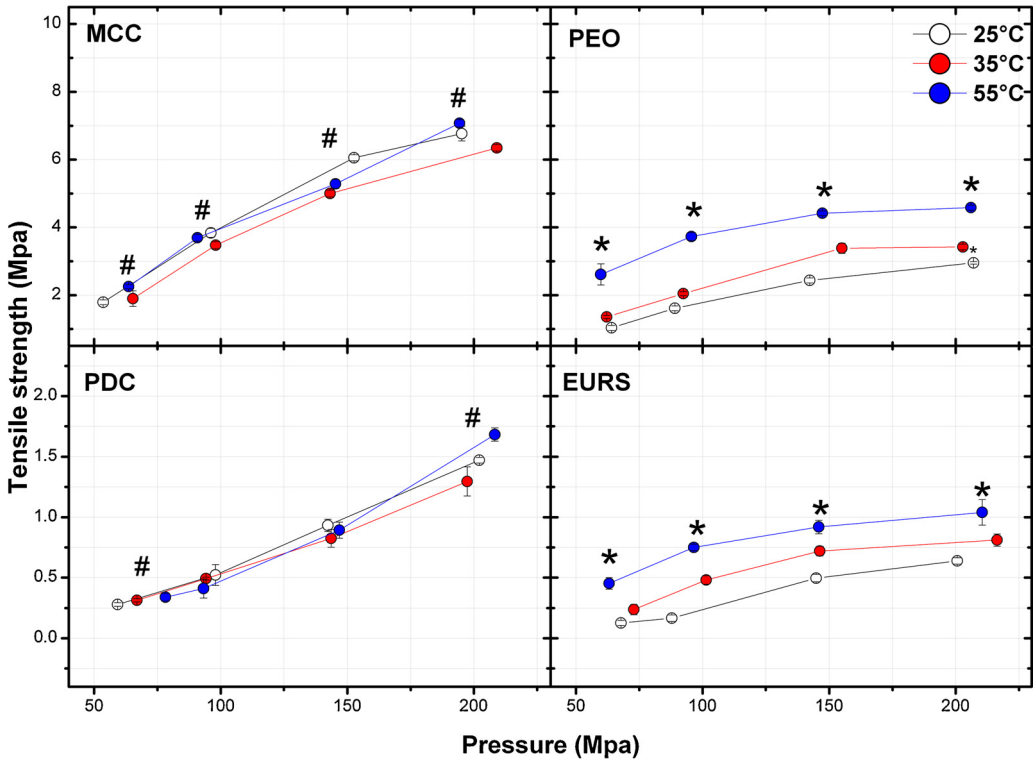

Fig. 6. Effect of the temperature and pressure on the tensile strength values of the tablets prepared with all the different materials. In order to highlight the differences on tablets hardness, the tensile strength values are reported using two different scales for the materials with different tabletability. Symbols * and # refer to statistical significance as reported in Section 2.5. Tablets and compaction data analysis.

improved the tabletability thank to the increase of mechanical and chemical interparticle bonds. From the other side, energy analysis is only able to explain the general trend of tablets hardness, failing in discrimination on the effect of temperature.

In the case of PEO, the increase in tabletability can also be attributed to a higher bounds formation through the mechanism of cold welding.

4. Conclusion

The obtained results reveal that temperature represents a crucial parameter for the manufacturing of tablets composed of materials characterized by thermal transition at low temperature. Particularly, these excipients showed a variation of tabletability as a consequence of a different ductility at the different temperatures.

According to these results, a preliminary thermal analysis (DSC, DMA, etc.) appears to be a useful tool in order to detect temperature sensitive materials. However, thermal analysis does not provide any information concerning the real effect of temperature on the materials compression properties and on mechanical features of tablets. Such information can be only obtained simulating the real compaction process. Moreover, the knowledge of the influence of temperature on the compaction behaviour of materials (Heckle analysis) is valuable information to solve the concerns due to formulation scale-up, improving the general robustness of the whole production process.

Thus, a modified tableting machine, as that used in this work, represents a powerful instrument in order to provide useful information at an early stage, concerning any problems related to temperature increase, during the development of tablets formulations.

References

Abdel-Halim, H., Traini, D., Hibbs, D., Gaisford, S., Young, P., 2011. Modelling of molecular phase transitions in pharmaceutical inhalation compounds: an in silico approach. Eur. J. Pharm. Biopharm. 78, 83–89.

Abiad, M.G., Gonzalez, D.C., Mert, B., Campanella, O.H., Carvajal, M.T., 2010. A novel method to measure the glass and melting transitions of pharmaceutical powders. Int. J. Pharm. 396, 23–29.

Bechard, S.R., Down, G.R.B., 1992. Infrared imaging of pharmaceutical materials undergoing compaction. Pharm. Res. 9, 521–528.

Buckner, I.S., Friedman, R.A., Wurster, D.E., 2010. Using compression calorimetry to characterize powder compaction behavior of pharmaceutical materials. J. Pharm. Sci. 99, 861–870.

Celik, M., Marshal, K., 1989. Use of a compaction simulator system in tabletting research. Drug Dev. Ind. Pharm. 15, 759–800.

Cespi, M., Misici-Falzi, M., Bonacucina, G., Ronchi, S., Palmieri, G.F., 2008. The effect of punch tilting in evaluating powder densification in a rotary tablet machine. J. Pharm. Sci. 97, 1277–1284.

Cunha-Filho, M.S.S., Martínez-Pacheco, R., Landín, M., 2007. Compatibility of the antitumoral β-lapachone with different solid dosage forms excipients. J. Pharm. Biomed. Anal. 45, 590–598.

de Blaey, C.J., Weekers-Andersen, A.B., Polderman, J., 1971. Compression of pharmaceuticals. V. Formulation development of a new compound with the aid of quantitative force–displacement measurements. Pharm. Weekbl. 106, 893–903.

DeCrosta, M.T., Schwartz, J.B., Wigent, R.J., Marshall, K., 2000. Thermodynamic analysis of compact formation; compaction, unloading, and ejection. I. Design and development of a compaction calorimeter and mechanical and thermal energy determinations of powder compaction. Int. J. Pharm. 198, 113–134.

DeCrosta, M.T., Schwartz, J.B., Wigent, R.J., Marshall, K., 2001. Thermodynamic analysis of compact formation; compaction, unloading, and ejection. II. Mechanical energy (work) and thermal energy (heat) determinations of compact unloading and ejection. Int. J. Pharm. 213, 45–62.

Doldán, C., Souto, C., Concheiro, A., Martínez-Pacheco, R., Gómez-Amoza, J.L., 1995. Dicalcium phosphate dihydrate and anhydrous dicalcium phosphate for direct compression: a comparative study. Int. J. Pharm. 124, 69–74.

Duberg, M., Nyström, C., 1986. Studies on direct compression of tablets. XVII. Porosity–pressure curves for the characterization of volume reduction mechanisms in powder compression. Powder Technol. 46, 67–75.

Emeje, M.O., Isimi, C.Y., Kunle, O.O., Ofoefule, S.I., 2007. Effect of polyethylene glycol and sodium lauryl sulphate on the compaction characteristics of Eudragit and drug release from its matrix. J. Appl. Sci. 7, 2598–2603.

Fell, J.T., Newton, J.M., 1970. Determination of tablet strength by the diametral-compression test. J. Pharm. Sci. 59, 688–691.

Fell, J.T., Newton, J.M., 1971. Effect of particle size and speed of compaction on density changes in tablets of crystalline and spray-dried lactose. J. Pharm. Sci. 60, 1866–1869.

Fujimori, J., Yonemochi, E., Fukuoka, E., Terada, K., 2002. Application of Eudragit RS to thermo-sensitive drug delivery systems. I. Thermo-sensitive drug release from acetaminophen matrix tablets consisting of Eudragit RS/PEG 400 blend polymers. Chem. Pharm. Bull. 50, 408–412.

Hanus, E.J., King, L.D., 1968. Thermodynamic effects in the compression of solids. J. Pharm. Sci. 57, 677–684.

Heckel, R.W., 1961a. An analysis of powder compaction phenomena. Trans. Metall. Soc. AIME 221, 1001–1008.

Heckel, R.W., 1961b. Density–pressure relationships in powder compaction. Trans. Metall. Soc. AIME 221, 671–675.

Kapoor, R., Nemat-Nasser, S., 1998. Determination of temperature rise during high strain rate deformation. Mech. Mater. 27, 1–12.

Ketolainen, J., Ilkka, J., Paronen, P., 1993. Temperature changes during tabletting measured using infrared thermoviewer. Int. J. Pharm. 92, 157–166.

Klinzing, G.R., Zavaliangos, A., Cunningham, J., Mascaro, T., Winstead, D., 2010. Temperature and density evolution during compaction of a capsule shaped tablet. Comput. Chem. Eng. 34, 1082–1091.

Levin, M., 2001. Pharmaceutical Process Scale-Up. Marcel Dekker, Inc., New York.

Menard, K.P., 1999. Dynamic Mechanical Analysis: A Practical Introduction. CRC Press, London.

Michaut, F., Busignies, V., Fouquereau, C., Huet De Barochez, B., Leclerc, B., Tchoreloff, P., 2010. Evaluation of a rotary tablet press simulator as a tool for the characterization of compaction properties of pharmaceutical products. J. Pharm. Sci. 99, 2874–2885.

Mura, P., Manderioli, A., Bramanti, G., Furlanetto, S., Pinzauti, S., 1995. Utilization of differential scanning calorimetry as a screening technique to determine the compatibility of ketoprofen with excipients. Int. J. Pharm. 119, 71–79.

Nelson, E., Busse, L.W., Higuchi, T., 1955. The physics of tablet compression. VII. Determination of energy expenditure in the tablet compression process. J. Pharm. Sci. 44, 223–225.

Palmieri, G.F., Joiris, E., Bonacucina, G., Cespi, M., Mercuri, A., 2005. Differences between eccentric and rotary tablet machines in the evaluation of powder densification behaviour. Int. J. Pharm. 298, 164–175.

Pedersen, S., Kristensen, H.G., 1994. Change in crystal density of acetylsalicylic acid during compaction. S.T.P. Pharma Sci. 4, 201–206.

Picker, K.M., 2000. Three-dimensional modeling to determine properties of tableting materials on rotary machines using a rotary tableting machine simulator. Eur. J. Pharm. Biopharm. 50, 293–300.

Picker-Freyer, K.M., 2006. Polyethylene oxides: analysis of tablet formation and properties of the resulting tablets. J. Therm. Anal. Calorim. 85, 495–504.

Ragnarsson, G., Sjögren, J., 1983. Work of friction and net work during compaction. J. Pharm. Pharmacol. 35, 201–204.

Ragnarsson, G., Sjögren, J., 1985. Force–displacement measurements in tableting. J. Pharm. Pharmacol. 37, 145–150.

Rouéche, E., Serris, E., Thomas, G., Périer-Camby, L., 2006. Influence of temperature on the compaction of an organic powder and the mechanical strength of tablets. Powder Technol. 162, 138–144.

Royall, P.G., Huang, C.Y., Tang, S.W., Duncan, J., Van-de-Velde, G., Brown, M.B., 2005. The development of DMA for the detection of amorphous content in pharmaceutical powdered materials. Int. J. Pharm. 301, 181–191.

Schwartz, J.B., 2001. Scale-up of the compaction and tableting process. In: Levin, M. (Ed.), Pharmaceutical Process Scale-Up. Marcel Dekker, Inc., New York, pp. 221–237.

Sonnergaard, J.M., 1999. A critical evaluation of the Heckel equation. Int. J. Pharm. 193, 63–71.

Tatavarti, A.S., Muller, F.X., Hoag, S.W., 2008. Evaluation of the deformation behavior of binary systems of methacrylic acid copolymers and hydroxypropyl methylcellulose using a compaction simulator. Int. J. Pharm. 348, 46–53.

Travers, D.N., Merriman, M.P., 1970. Temperature changes occurring during the compression and recompression of solids. J. Pharm. Pharmacol. 22, 11S/16S.

Van Der Voort Maarschalk, K., Zuurman, K., Van Steenbergen, M.J., Hennink, W.E., Vromans, H., Bolhuis, G.K., Lerk, C.F., 1997. Effect of compaction temperature on consolidation of amorphous copolymers with different glass transition temperatures. Pharm. Res. 14, 415–419.

Verma, R.K., Garg, S., 2005. Selection of excipients for extended release formulations of glipizide through drug–excipient compatibility testing. J. Pharm. Biomed. Anal. 38, 633–644.

Windbergs, M., Strachan, C.J., Kleinebudde, P., 2009. Influence of structural variations on drug release from lipid/polyethylene glycol matrices. Eur. J. Pharm. Sci. 37, 555–562.

Yang, L., Venkatesh, G., Fassihi, R., 1996. Characterization of compressibility and compactibility of poly(ethylene oxide) polymers for modified release application by compaction simulator. J. Pharm. Sci. 85, 1085–1090.

Yap, S.F., Adams, M.J., Seville, J.P.K., Zhang, Z., 2008. Single and bulk compression of pharmaceutical excipients: evaluation of mechanical properties. Powder Technol. 185, 1–10.

Zavaliangos, A., Galen, S., Cunningham, J., Winstead, D., 2008. Temperature evolution during compaction of pharmaceutical powders. J. Pharm. Sci. 97, 3291–3304.

Zlokarnik, M., 2001. Dimensional analysis and scale-up in theory and industrial application. In: Levin, M. (Ed.), Pharmaceutical Process Scale-Up. Marcel Dekker, Inc., New York, pp. 1–43.