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Original predictive approach to the compressibility of pharmaceutical powder mixtures based on the Kawakita equation

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ABSTRACT

In the pharmaceutical industry, tablets are obtained by the compaction of two or more components which have different physical properties and compaction behaviours. Therefore, it could be interesting to predict the physical properties of the mixture using the single-component results. In this paper, we have focused on the prediction of the compressibility of binary mixtures using the Kawakita model. Microcrystalline cellulose (MCC) and L-alanine were compacted alone and mixed at different weight fractions. The volume reduction, as a function of the compaction pressure, was acquired during the compaction process ("in-die") and after elastic recovery ("out-of-die"). For the pure components, the Kawakita model is well suited to the description of the volume reduction. For binary mixtures, an original approach for the prediction of the volume reduction without using the effective Kawakita parameters was proposed and tested. The good agreement between experimental and predicted data proved that this model was efficient to predict the volume reduction of MCC and L-alanine mixtures during compaction experiments.

1. Introduction

In the pharmaceutical industry, tablets are obtained by the compaction of two or more components (active substances and excipients) which have different physical properties and compaction behaviours. But, even if compaction is a common pharmaceutical operation, most studies are performed on single components as a result of the complexity of the compression process. Data on single materials are generally available but, the final formulation results from many trials. Therefore, it would be helpful to predict the mixture behaviour from the data obtained with the pure components. Numerous works have studied the compaction of binary mixtures (Busignies et al., 2006a; Ilkka and Paronen, 1993; Zheng et al., 1995). It has been observed that the densification and compaction behaviours of mixtures are influenced by the characteristics of the pure components and by the mass fractions of each component in the mixture. The percolation theory is sometimes used to explain the changes of properties of compacted binary mixtures (Leuenberger, 1999). It is a composition percolation phenomenon in which the important parameter is the phase fraction. Moreover, in binary mixtures, three kinds of interactions may occur between the two compounds (Leuenberger, 1982). The properties of mixtures depend on the relative concentration and the relative bond-forming properties (Holman, 1991). However, very little is known about the interactions between the particles of different materials, and the tablets made from mixtures may have different properties from those produced from single components (Busignies et al., 2006a,b; Ilkka and Paronen, 1993; Van Veen et al., 2000). Moreover, in most cases, no simple relationship was found using the properties of the single materials and their concentrations in the mixture.

To study the behaviour under pressure, global models are often used in the pharmaceutical field like for example the Heckel model (Heckel, 1961a,b) or the Kawakita model (Kawakita and Lüdde, 1970/71; Kawakita and Tsutsumi, 1966). Compression parameters are derived from these models and are used in pharmaceutical formulation to describe, with a numerical value, the behaviour of powder under pressure. In the case of mixtures, some works proposed mixing rules derived from these parameters (Busignies et al., 2006a; Frenning et al., 2009; Ilkka and Paronen, 1993). The results of these works were generally inconsistent. Linear and non-linear relationships were observed from the compression parameters of the single materials and their proportions in the mixture (Busignies et al., 2006a; Frenning et al., 2009; Ilkka and Paronen, 1993; Larhrib and Wells, 1997, 1998; Van Veen et al., 2000).

Recently, the Kawakita equation was brought in for single materials with a proposal of physical interpretation of the Kawakita parameters (Denny, 2002; Nordstrom et al., 2008; Sonnergaard, 2001). For a single material, this equation is written (Kawakita and

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Lüdde, 1970/71; Kawakita and Tsutsumi, 1966):

$$C = \frac{abP}{1+bP} \quad (1)$$

where C is the relative volume decrease under the pressure P:

$$C = \frac{V_0 - V}{V_0} = \frac{\Delta V}{V_0} \quad (2)$$

a and b are the Kawakita parameters, and V_0 the initial apparent volume of powder. a and $1/b$ represent the relative volume decrease at an infinite pressure and the applied pressure needed to achieve a relative volume decrease of $a/2$, respectively.

Eq. (1) is often written using the linear expression of the Kawakita equation (Kawakita and Lüdde, 1970/71; Kawakita and Tsutsumi, 1966):

$$\frac{P}{C} = \frac{1}{ab} + \frac{P}{a} \quad (3)$$

For ideal binary mixtures, Frenning et al. (2009) proposed a mixing law for the Kawakita parameters. This law will be further discussed below.

The objective of this work was to apply the Kawakita equation to mixtures of L-alanine and microcrystalline cellulose (MCC). These two model compounds were chosen for several reasons. First, MCC and L-alanine are both plastic materials but differ in the decrease of porosity under pressure. Moreover, tablets of MCC and L-alanine differ in their crushing strength. In fact, the cohesion of L-alanine tablets is very poor contrary to MCC tablets (the diametral tensile strength of tablets obtained under 150 MPa is 0.29 MPa for L-alanine and 1.70 MPa for MCC). Finally, L-alanine and MCC can be easily differentiated by IR spectroscopy. This is an important point for the evaluation of the homogeneity of powder mixtures.

Firstly, Eq. (3) was used with the two single-component materials with the data obtained under pressure ("in-die" data) and after total elastic recovery ("out-of-die" data). Secondly, this equation was used to describe the compaction behaviour of binary mixtures of L-alanine and microcrystalline cellulose. To validate the approach proposed by Frenning et al., the experimental data were compared with the predictions derived from Frenning et al. (2009). Analysis of these results enabled us to put forward another model for the prediction of the volume reduction of binary mixtures.

2. Materials and methods

2.1. Materials

The two materials were a microcrystalline cellulose, MCC (Vivapur 12®, 5601250730, JRS Pharma, Rosenberg, Germany, kindly given by JRS Pharma) and L-alanine (Merck KGaA, Darmstadt, Germany). To reduce the impact of the particle size, the two materials were first prepared to obtain similar particle size fractions. MCC was sieved using a mechanical sieve shaker (Tamisor®, Paris, France) between 125 and 315 μm. L-alanine was first ground (Ika® A10, Imlab, Lille, France) and secondly sieved as previously described for MCC. Particles of both MCC and L-alanine were checked to verify that they had similar morphologies (Fig. 1a and b). The particle size distribution in volume (%) of the sieved fractions was obtained by laser diffraction (Mastersizer 2000®, Malvern Instruments, Worcestershire, UK) in accordance with Fraunhofer's theory. As seen in Fig. 1c, the distribution in volume of the two materials is rather similar.

MCC and L-alanine were lubricated with 0.5% (w/w) of magnesium stearate MF3V® (Peter Greven, Bad Münstereifel, Germany) using a Turbula mixer (type T2C, Willy A Bachofen, Muttenz, Switzerland) at 50 rpm for 5 min. The apparent particle density of the lubricated fractions was determined using a helium pycnometer (AccuPyc 1330, Micromeritics, Norcross, GA, USA), see Table 1. The measurements were performed in triplicate (10 purges and 10 runs) using fresh samples each time.

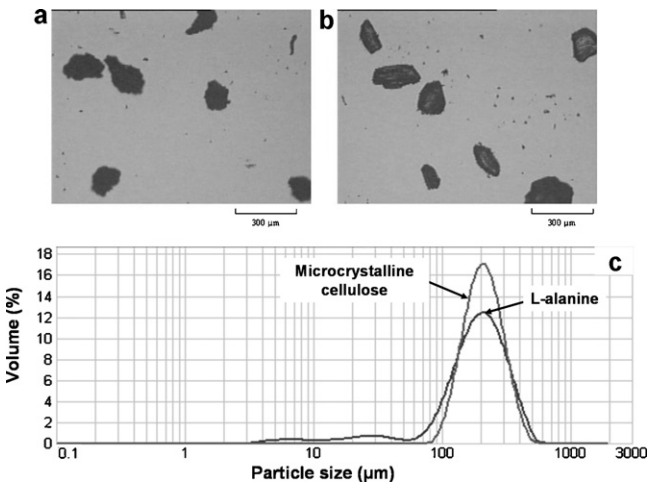

Fig. 1. Optic microscopy images of (a) microcrystalline cellulose, (b) L-alanine and (c) particle size distribution in volume for the two components (MCC: mode = 209 μm and D[4;3] = 221 μm; L-alanine: mode = 208 μm and D[4;3] = 204 μm).

2.2. Binary mixtures

The lubricated fraction of L-alanine and MCC were then used to prepare binary mixtures in several mass percentages (15/85, 35/65, 50/50, 65/35, 85/15 (w/w)) with a Turbula® mixer (type T2C, Willy A Bachofen, Switzerland) at 50 rpm for 2 min. The apparent particle density of the mixtures was determined as previously described for single materials (Table 1).

2.3. Attenuated total reflectance (ATR) infrared spectroscopy

The homogeneity of the binary mixtures was checked by IR spectroscopy with a PerkinElmer Spectrum One FT-IR spectrometer (Perkin Elmer, USA). A diamond ATR accessory was used for all the experiments. As we worked on binary mixtures, it was only necessary to quantify one of the components and we chose to quantify L-alanine. For this purpose we worked in aqueous solution using the fact that L-alanine is highly soluble in water and that MCC and magnesium stearate have very low solubility in water. The method is thus based on the determination of alanine concentration in water. The experiments were performed by pouring a drop of solution on the ATR crystal, and we first traced a calibration curve using solutions of known L-alanine concentration (between 0 and 100 mg cm^{-3}). The height of the peak at 1594 cm^{-1} was used to quantify L-alanine. Then, for each mixture, 281 ± 35 mg (n = 15) of powder was poured into water. This amount of mixture was lower than the mass corresponding to the tablets (Table 1). The samples were taken with a spatula from the top, middle and bottom of the container. The same method was used to pour the powder into the die. Knowing the mass of the powder poured into the water and the final concentration in L-alanine of the solution, it was thus possible to calculate the effective mass ratio in the sample. Each spectrum comprised 8 scans measured at a spectral resolution of 4 cm^{-1} in the 4000–550 cm^{-1} range. Spectral data were acquired with Spectrum software (Perkin Elmer, USA). Three spectra were obtained for each sample and the measurements were performed in triplicate with new samples each time.

Table 1
Apparent particle densities for lubricated L-alanine, lubricated microcrystalline cellulose and their binary mixtures ($n = 3$) and masses of the tablets ($n = 40$ with exception for L-alanine, $n = 25$ and L-alanine/MCC 85/15 (w/w), $n = 35$).

L-Alanine/MCC[a] (%, w/w)	100/0	85/15	65/35	50/50	35/65	15/85	0/100
Apparent particle density ($g\,cm^{-3}$)[b]	1.3642 ± 0.0002	1.3926 ± 0.0006	1.4287 ± 0.0008	1.4561 ± 0.0006	1.4832 ± 0.0008	1.5202 ± 0.0012	1.5455 ± 0.0013
Tablet's mass (mg)	688 ± 3	632 ± 4	561 ± 2	514 ± 2	475 ± 3	430 ± 2	415 ± 3

[a] L-Alanine and MCC were lubricated with 0.5% (w/w) of magnesium stearate.
[b] Apparent particle density measured using a helium pycnometer (AccuPyc 1330, Micromeritics, Norcross, GA, USA).

2.4. Compaction

Cylindrical tablets of single components and binary mixtures were manufactured using an eccentric instrumented Frogerais OA tableting press (Busignies et al., 2004). The compression forces were measured with sensors on the upper and lower punches and were calibrated using an external extensometric gauged line. The displacements of the punches were obtained from displacement sensors put on the upper and lower punches. The zero value of displacements was set for a die height of exactly 1 cm. Then, the displacements were calibrated using wedges of precise known heights. The accuracy of the punch displacements was 0.001 mm. The sampling rate was 1000 Hz. The global elastic deformation was taken into account and was determined by compacting manually a non-deformable wedge (Michaut et al., 2010). The cylindrical die of 1 cm^3 (section of 1 cm^2 and height of 1 cm) was manually filled. Tablets were manufactured under various degrees of compaction pressure (between 40 and 200 MPa). The vertical compaction speed was about 80 mm s^{-1} (speed when the upper punch enters the die). If the dwell-time was defined by the time when the compaction force was maintained between 90% and 100% of its maximum value, its value is approximately 50–60 ms. At each chosen compaction pressure, five tablets were obtained. The compression forces and the punch displacements were recorded using Pecamec software (4.2 version, J2P instrumentation, France).

The mechanism of deformation of the two materials was studied using the Heckel model (Heckel, 1961a,b). The mean yield pressure (P_y in MPa) is the reciprocal of the linear part of the Heckel curve. In this work, the P_y values were obtained with the "in-die" method (*i.e.* under pressure). The regression on the linear region was performed based on the method of least squares ($R^2 > 0.99$). The ranges of determination for the linear zone of the Heckel plots were from 40 to 100 MPa for MCC (Busignies et al., 2006a) and from 40 to 90 MPa for L-alanine. The two materials consolidated by plastic deformation since the mean yield pressures deduced from the plots are about 55 MPa for MCC (Busignies et al., 2006a) and 90 MPa for L-alanine (S. Duca, unpublished results. The study of compaction mixing laws and characterization by IR microscopy, Master Pharmacotechnie et Biopharmacie, Univ Paris-Sud, 2010).

After compaction, the tablets were stored at room temperature and at 50% of relative humidity. After total elastic recovery, the compacts were weighed (Sartorius BP 2215, Germany) and measured with a micrometer having an accuracy of 1 μm (Digimatic 293, Mitutoyo, Japan).

3. Results and discussion

3.1. Compressibility of pure products

Before the compression of binary mixtures, the two compounds were studied as pure products (with 0.5% (w/w) of magnesium stearate). These experiments were the basis of the modeling for the behaviour of mixtures. Thanks to the instrumentation of the press, it was possible to follow the volume reduction during the compression experiment. This provided the so-called "in-die" data. Moreover, each obtained compact was kept, after the experiment, at 50% of relative humidity and at room temperature for 48 h. Then, the volume of the compact was measured. Compacts were obtained for a large range of pressure, and thanks to these experiments, the "out-of-die" evolution of the volume as a function of the pressure was plotted.

For both products, "in-die" and "out-of-die" results were fitted using the Kawakita model (Eq. (3)). This model requires the determination of the parameter V_0 which represents the initial apparent volume of powder, at the end of rearrangement and stack-

Table 2
Kawakita parameters obtained for the single-component materials from "in-die" and "out-of-die" data.

	V_0 (cm^3)	"in-die"		"out-of-die"	
		a (n = 5)	b (MPa^{-1})(n = 5)	a	b (MPa^{-1})
L-Alanine[a]	0.844 ± 0.003	0.411 ± 0.001	0.060 ± 0.002	0.350	0.070
MCC[a]	0.760 ± 0.004	0.705 ± 0.001	0.057 ± 0.001	0.653	0.042

[a] L-Alanine and MCC were lubricated with 0.5% (w/w) of magnesium stearate.

ing stage. In the literature, this volume is generally measured in die by recording the powder bed height at a fixed applied pressure at the beginning of the compression (Nordstrom et al., 2008; Sonnergaard, 2000). Sonnergaard (2001) suggested calculating the initial volume but observed in the same work that the V_0 values correspond to a pressure of 1–2 MPa. In our case, we chose to measure V_0 for a pressure of 1.5 MPa. The values of V_0 at this pressure are reported in Table 2.

It is important to note that the chosen value of V_0 has an influence on the values of the fitting parameters a and b of the Kawakita model but not on the quality of the fit. The two parameters a and b are then dependant on V_0. This important point will be discussed later. Finally, the b parameter seems to be more affected by a change of the initial volume than the a parameter (Sonnergaard, 2000).

The plot of the Kawakita model (Eq. (3)) and the experimental curves for both products for "in-die" and "out-of-die" data can be seen in Fig. 2. In all the cases, the Kawakita equation fits the experimental data well, on the whole range of pressures. The parameters a and b which fit are shown in Table 2. These values are slightly different from those published (Frenning et al., 2009; Nordstrom et al., 2008) and close to those proposed by Sonnergaard (2001). As the parameters a and b are dependent on the V_0 value, a difference was expected. It is also difficult to compare works based on the use of completely different materials ((Frenning et al., 2009) used even mm-sized spherical agglomerates). These values were then used to study binary mixtures.

3.2. Study of the binary mixtures

3.2.1. Homogeneity of the mixtures

Before the compression experiment, it was important to ensure the homogeneity of the mixture to obtain compacts with accurate

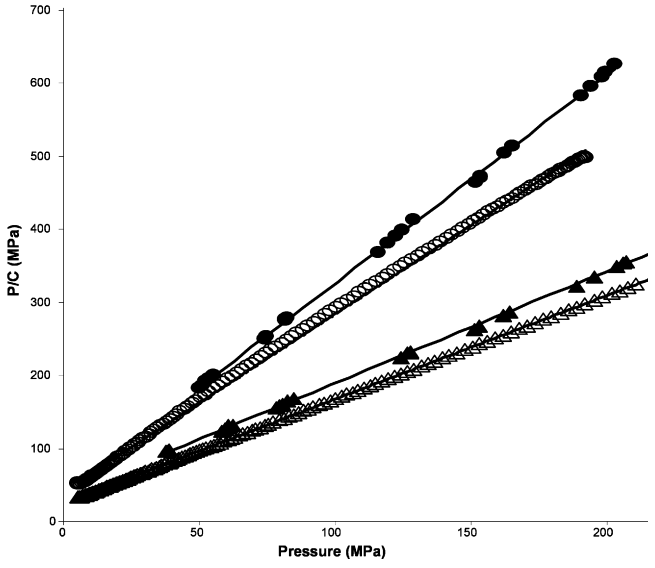

Fig. 2. Example of linearisation of the experimental data using the Kawakita equation (Eq. (3)). The solid line represents linear fits to the data. Key: (○) L-alanine, "in-die" data, R^2 = 0.9989; (●) L-alanine, "out-of-die" data, R^2 = 0.9994; (△) MCC, "in-die" data, R^2 = 1.0; (▲) MCC, "out-of-die" data, R^2 = 0.9997.

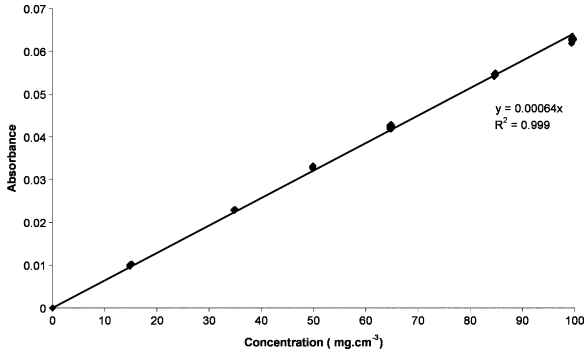

Fig. 3. Calibration curve obtained by measuring infrared spectra of solutions of L-alanine (absorbance at 1594 cm^{-1}). For each concentration, n = 9.

composition homogeneity during compression experiments. After mixing the two powders, L-alanine content was tested by infrared spectroscopy as described above. A good linearity was obtained as is shown on the calibration curve. See Fig. 3. The different mixtures were then studied. Three samples of each mixture were each measured threefold. The results are presented in Table 3. A good agreement was achieved between the theoretical and experimental percentages. This experiment ensured the efficiency of the mixing protocol.

3.2.2. Volume evolutions

The model proposed by Frenning et al. (2009) was based on the assumption that volume may be considered an additive property, which leads to the following equation:

$$V_{\text{mix}} = \sum_i V_i \tag{4}$$

where V_{mix} is the volume of the mixture and V_i the volume of component i. This means that each component in the mixture behaves as if it was compressed alone. We, first of all, checked this hypothesis, both "in-die" and "out-of-die" for different pressure targets.

To calculate the theoretical volume at xMPa (V^x_{mix}) we used the following equation:

$$V^x_{\text{mix}} = V^x_1 + V^x_2 = \frac{m_1}{\rho^x_1} + \frac{m_2}{\rho^x_2} = m_{cp}\left(\frac{X_1}{\rho^x_1} + \frac{1 - X_1}{\rho^x_2}\right) \tag{5}$$

where V^x_1 and V^x_2 are the volume of the compounds 1 and 2 at xMPa; m_{cp}, m_1 and m_2 are respectively the mass of the compact, of compounds 1 and 2 in the compact; X_1 is the mass fraction of compound

Table 3
Proportions of L-alanine determined by ATR infrared spectroscopy.

L-Alanine/MCC[a] (%, w/w)	Proportion in mass (%) determined by ATR infrared spectroscopy
15/85	14.5 ± 0.2
35/65	34.8 ± 0.2
50/50	50.6 ± 0.9
65/35	66.0 ± 0.4
85/15	83.0 ± 1.3

[a] L-Alanine and MCC were lubricated with 0.5% (w/w) of magnesium stearate.

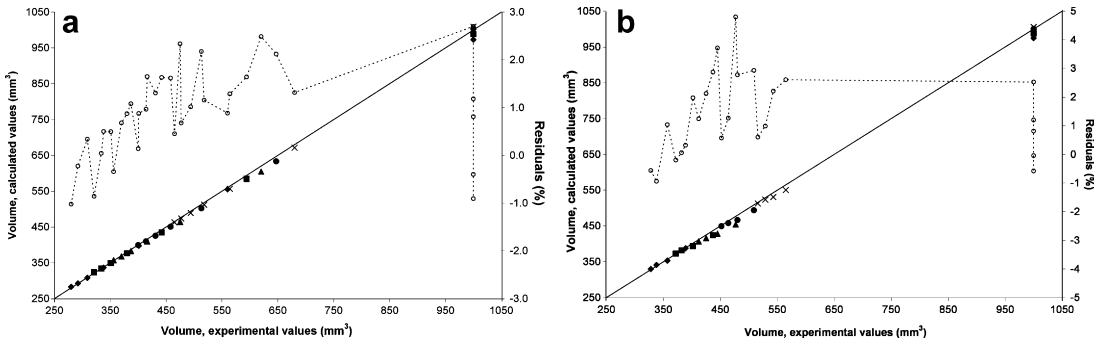

Fig. 4. Comparison between experimental volumes and calculated volumes for binary mixtures, (a) "in-die" and (b) "out-of-die". $n = 5$ for pressure values of 0, 10, 40, 80, 120, 160 and 200 MPa. Key: (♦) L-alanine/MCC 15/85 (w/w); (■) L-alanine/MCC 35/65 (w/w); (▲) L-alanine/MCC 50/50 (w/w); (●) L-alanine/MCC 65/35 (w/w); (×) L-alanine/MCC 85/15, (w/w) (left axis). Residuals calculated from Eq. (6) (○, right axis).

1 in the mixture; ρ_1^x and ρ_2^x are the apparent density of compound 1 and 2 at *x*MPa obtained from the compression experiments of pure products.

The graph shown in Fig. 4 represents, for the mixtures, the plot of the experimental volume obtained from the compaction experiments *versus* the theoretical volume predicted from Eq. (5). The $y = x$ curve was added onto the graph to make the comparison easier. The residuals (R) were calculated as a percentage with the following equation:

$$R = \frac{x_{obs} - x_{calc}}{x_{obs}} \times 100 \quad (6)$$

where x_{obs} and x_{calc} are respectively the observed and calculated values.

A good alignment of the points along the curve was obtained, for both "in-die" and "out-of-die" results. The residuals were in a range of −1 to 3% for the "in-die" values and −1 to 5% for the "out-of-die" volumes (a limit of ±5% was chosen as an acceptable level). The hypothesis can now be used for further developments.

3.2.3. Frenning model for the effective Kawakita parameters

Frenning et al. (2009) proposed a model to obtain the effective parameters of the Kawakita equation for binary mixtures. Their model is first based on the additive property of the volume. Using this property, the model predicts that the effective parameter a of the mixture can be obtained as follows:

$$a_{mix} = \sum_i \upsilon_i a_i \quad (7)$$

where a_i is the Kawakita parameter of compound i and υ_i is the initial volume fraction of this compound.

For each mixture, we calculated the expected effective Kawakita parameter a_{mix} according to this equation and compared it to the Kawakita parameter found by fitting the mixture data using the Kawakita model. The results for "in-die" and "out-of-die" data can be seen in Fig. 5. The residuals (obtained from Eq. (6)) are, in all the cases, higher than zero, but at an acceptable level (in a range of 0.9–2.1% for the "in-die" values and 1.6–5.4% for the "out-of-die" values). This means that the experimental values are slightly higher than the predicted values. Nevertheless, examining the residual values (close or lower than 5%), a good agreement between theoretical and experimental parameters was concluded.

For the effective parameter b_{mix}, the problem is more difficult. Frenning et al. introduced another hypothesis to define a law which is $b_i P \gg 1$. This leads to a relation which is:

$$\frac{1}{b_{mix}} = \frac{1}{a_{mix}} \sum_i \frac{\upsilon_i a_i}{b_i} \quad (8)$$

where a_i and b_i are the Kawakita parameters of compound i and υ_i is the initial volume fraction of this compound.

But, according to the results presented previously, b_i has values around 5×10^{-2} MPa^{-1}. This means that to obtain, $b_i P = 10$ a pressure around 200 MPa would have to be reached which corresponds to the upper part of the pressure range. Then, this hypothesis was not expected to be applicable to the whole pressure range.

For each mixture, we compared the experimental values of b and the predicted values according to Frenning's model. The results presented in Fig. 6 show that the law does not predict correctly the evolution of the b parameters obtained when Eq. (3) was used for binary mixtures, especially in the case of the "out-of-die" experiments (residuals in a range of 2–7.3% for the "in-die" values but in a range of 7–37.3% for the "out-of-die" values).

According to our results, the model defined by Frenning et al. is not well suited to the prediction of the effective Kawakita parameters of our binary mixtures. Another approach was then defined.

3.2.4. Model for the prediction of the volume reduction of binary mixtures

The previous model was based on the prediction of the effective Kawakita parameters. But, as discussed above, a and b are dependent on the V_0 value and cannot be considered as an intrinsic property of the material. Moreover, physical interpretations of the parameter values in terms of mechanical properties are not obvious (Nordstrom et al., 2008). We therefore decided to develop another approach to predict the volume reduction without using effective Kawakita parameters. This approach is based, as is the Frenning model (Frenning et al., 2009), on the hypothesis of additive volumes (see Eq. (4)).

Thanks to this hypothesis, we can establish the same kind of equation for the volume reduction from initial volume (V_0) to the volume at the pressure P:

$$\Delta V_{mix} = \sum_i \Delta V_i \quad (9)$$

For each component, we can apply Kawakita model:

$$\Delta V_i = \frac{a_i b_i P}{1 + b_i P} V_{0,\,i} \quad (10)$$

If we use the initial volume fraction defined before as: $\upsilon_i = V_{0,i}/V_{0,mix}$ we obtain:

$$\frac{\Delta V_i}{V_{0,\,mix}} = \frac{a_i b_i P}{1 + b_i P} \upsilon_i \quad (11)$$

Finally, using the previous equation, it is possible to calculate the relative volume reduction of the mixture C_{mix} using the following

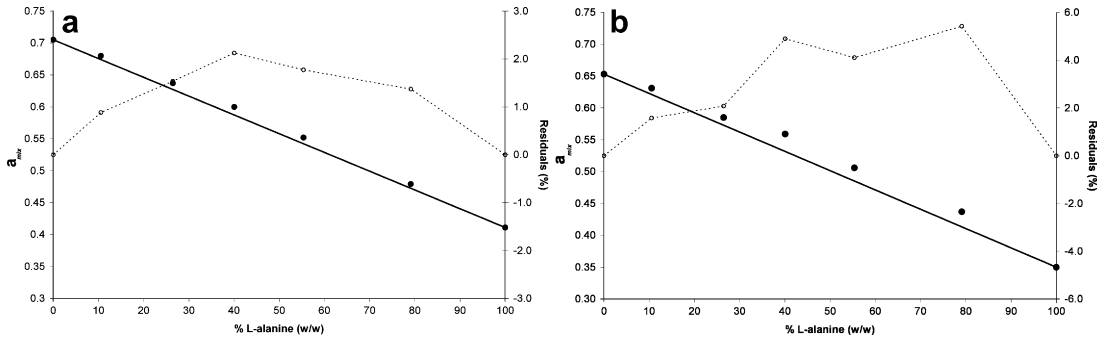

Fig. 5. Comparison between experimental data (symbols) of a_{mix} obtained (a) "in-die" or (b) "out-of-die" and predicted values (solid lines) from the mixing law proposed by Frenning et al. (2009). Residuals calculated from Eq. (6) (○, right axis).

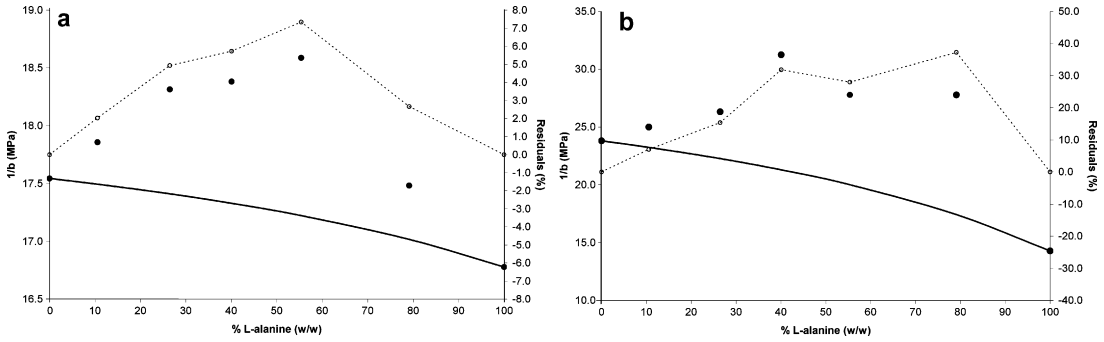

Fig. 6. Comparison between experimental data (symbols) of $1/b$ obtained (a) "in-die" or (b) "out-of-die" and predicted values (solid lines) from the mixing law proposed by Frenning et al. (2009). Residuals calculated from Eq. (6) (○, right axis).

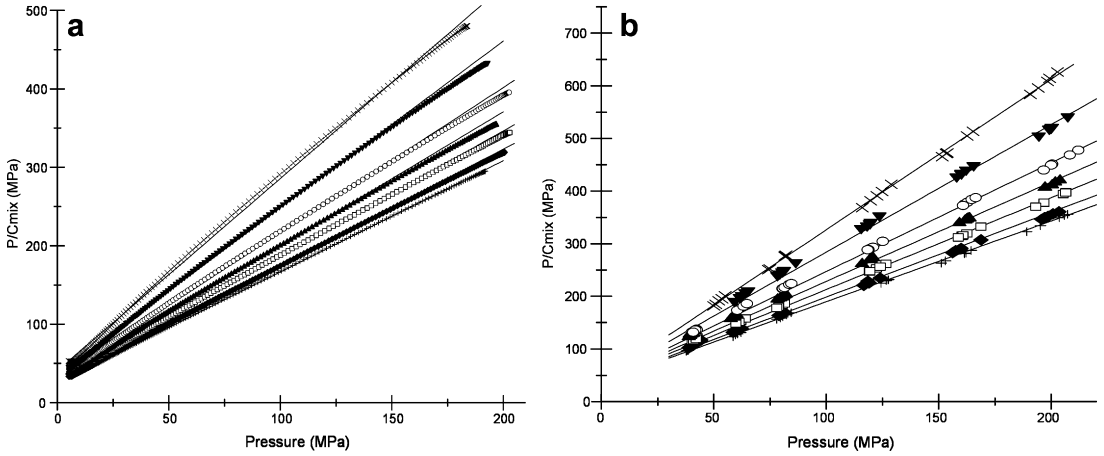

Fig. 7. Comparison between experimental data of P/C_{mix} (symbols) and model for the prediction of the volume reduction of binary mixture (solid lines). (a) "in-die"; (b) "out-of-die". Key: (+) L-alanine/MCC 0/100 (w/w); (♦) L-alanine/MCC 15/85 (w/w); (■) L-alanine/MCC 35/65 (w/w); (▲) L-alanine/MCC 50/50 (w/w); (●) L-alanine/MCC 65/35 (w/w); (▼) L-alanine/MCC 85/15 (w/w); (×) L-alanine/MCC 100/0 (w/w).

equation:

$$C_{mix} = \frac{\Delta V_{mix}}{V_{0,\,mix}} = \sum_i \frac{\Delta V_i}{V_{0,\,mix}} = \sum_i \frac{a_i b_i P}{1 + b_i P} \upsilon_i \tag{12}$$

In the case of a binary mixture we finally obtain the equation:

$$\frac{C_{mix}}{P} = \frac{a_1 b_1}{1 + b_1 P} \upsilon_1 + \frac{a_2 b_2}{1 + b_2 P} \upsilon_2 \tag{13}$$

Thanks to this last equation, it is then possible to calculate the volume reduction of the mixture under compression using the Kawakita parameters of the pure products (a_1, b_1 and a_2, b_2) and the initial volume fractions, but without requiring the effective Kawakita parameters (a_{mix} and b_{mix}).

The results of the model are shown in Fig. 7. There is a good agreement between the predictions and the experimental data for both "in-die" and "out-of-die" results. This approach, based on a simple hypothesis, is thus efficient to predict the volume reduction of the tested systems, as long as the additive property of the volume is valid. It is then possible to predict the volume of the powder during compression by using only the Kawakita parameters and the initial apparent volume of the pure products.

4. Conclusion

Based on the additive property of the volume, we propose in this paper an original approach to the volume reduction of the binary mixtures during compaction experiments. Contrary to the model

proposed by Frenning et al. (2009), our model was not based on the effective Kawakita parameters but it makes it possible to obtain the relative volume reduction of a mixture from the parameters of the single components. For both "in-die" and "out-of-die" experiments, a good agreement was found between experimental and predicted values. It proves that this model is efficient to predict the volume reduction of L-alanine and MCC binary mixtures during compaction experiments. This model was applied to two products having the same deformation behaviour and particle size which is a limitation for a practical application It now will be interesting to extent it to other components including brittle and small sized materials.

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