Study of the Compaction Mechanisms of Lactose-based Direct Compression Excipients using Indentation Hardness and Heckel Plots

MARIA DEL CARMEN MONEDERO PERALES, ANGEL MUÑOZ-RUIZ, MARIA VICTORIA VELASCO ANTEQUERA AND MARIA ROSA JIMÉNEZ-CASTELLANOS BALLESTEROS

Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, c/Tramontana s/n, Sevilla 41012, Spain

Abstract—Indentation hardness of tablet surfaces has been used to determine the consolidation mechanisms of the lactose-based excipients Fast Flo Lactose, Ludipress, Cellactose and Tablettose. The Leuenberger equation has been modified to obtain values of compressibility and compactability by using a value of compactability obtained from a tablet at maximum applied force and by substituting deformation resistance by relative deformation resistance. Also, parameters obtained from plots of the Heckel tablet-in-die and ejected-tablet methods were calculated in order to establish the comparative consolidation mechanisms in the lactose-based excipients under study. The possibility of using the absolute value of the difference between upper and lower surface hardnesses of the tablets made on an eccentric press is suggested as an alternative method to determine the comparative consolidation mechanisms of different substances.

The mechanical strength of material undergoing compression, tensile and shear stress is an important aspect in the control of the quality of pharmaceutical tablets and in any investigation into the process of compaction (Romano & Vázquez 1988; Fell & Newton 1970).

Various techniques have been used to assess tablet strength (Westbrook & Conrad 1973) including: static indentation, scratch, plowing, rebound, damping, cutting, abrasion, erosion and tablet tensile strength tests.

In order to explain better the mechanisms of tablet formation, there is now a greater tendency to investigate single particle deformation rather than the bulk deformation of a powder bed (Doelker 1988). In this sense, measurements of static indentation of tablets has been used to determine the compressibility and compactability of powders (Leuenberger 1982; Jetzer et al 1983).

Ridgway et al (1970) used a Brinell hardness tester which measured the depth of penetration directly by means of a displacement transducer. They showed that the indentation hardness was a maximum in the centre of the tablet face. Aulton (1981) concluded that the variation across the surface indicated that there was inefficient transmission of compression stresses through the mass during compaction. Jetzer (1986) suggested that useful information can be obtained by comparing hardness measurement and crushing strength, and that this data may help in the prediction of capping tendency.

Hardness testing using a pyramid (Vickers Hardness) instead of a ball to penetrate into the surface of the tablet under test can be compared with the data based on the Heckel plots ejected-tablet method (Fell & Newton 1971; Hersey & Rees 1973; Paronen 1986) or the tablet-in-die method (Humbert-Droz et al 1982).

Correspondence: M. C. Monedero Perales, Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, c/Tramontana s/n, Sevilla 41012, Spain.

Material and Methods

In this study, four lactose-based excipients for direct compression were used: Fast Flo Lactose, batch 3RJ 701 (Seppic, Paris, France); Ludipress, batch 56/0733 (BASF, Madrid, Spain); Cellactose, batch X945, and Tablettose, batch X101 (FHER SA, Madrid, Spain). All excipients were stored under controlled humidity conditions (r.h. = 40%) before use.

The true density of each powder was determined using a helium pycnometer (Model stereopycnometer, SPY3, Quantachrome, Syosset, NY, USA). Relative density on precompression (D_0) was measured using techniques described previously by Muñoz-Ruiz et al (1988). Compression characteristics of the powders were investigated using an instrumented single-punch tablet machine (Bonals AMT 300, Barcelona, Spain) fitted with strain gauges (HBM YL6) attached to dynamic amplifiers (NEC San-ei 6M81, Tokyo, Japan), inductive displacement transducers (HBM TS50, Darmstadt, Germany), digital amplifiers (HBM AB 12 with channels M55, Darmstadt, Germany), and via an analogue-to-digital converter Metrabyte DAS-16G1 (Metrabyte, MA, USA). Our own software (Muñoz-Ruiz 1992) was used for data acquisition and reduction. A quantity of powder to produce tablets of known thickness at zero theoretical porosity was weighed separately and filled manually into the die (12 mm). Flat compacts were prepared at seven different pressures corresponding to a range of crushing strengths between 0 and 200 N. Tablets were made after lubricating the die with a 5% w/v chloroformic solution of stearic acid. The tablet machine was run at 30 cycles min^{-1}.

To calculate tensile strength, crushing strength was determined immediately after compression using a commercially available crushing strength tester (Schleuniger-2E, Geneva, Switzerland) and the dimensions of the tablets were measured with a micrometer (Mitutoyo MDC-M293, Mitutoyo, Tokyo, Japan).

The diameter of the Vickers indentation was measured

Table 1. Indentation diameters (D in mm) and Vickers hardness (HV in MPa) of upper and lower surfaces of tablets prepared from a range of lactose-based excipients (average of three tablets and s.d.).

Excipient	Surface	Batch number					
		1	2	3	4	5	6
Fast Flo	Upper						
Lactose	D	0·684±0·011	0·359±0·002	0·314±0·008	0·271±0·010	0·253±0·009	0·220±0·010
	HV	19·40±0·6	71·14±12·5	92·61±4·2	124·5±11·6	142·8±10·9	188·1±19·8
	Lower						
	D	0·726±0·018	0·357±0·013	0·351±0·007	0·258±0·007	0·245±0·017	0·212±0·010
	HV	17·34±0·9	71·44±5·4	96·33±2·0	136·6±8·0	152·6±23·2	203·8±20·7
Ludipress	Upper						
	D	0·371±0·022	0·289±0·008	0·275±0·002	0·280±0·003	0·238±0·008	0·232±0·004
	HV	66·83±8·1	109·7±6·0	121·2±3·0	116·7±3·0	161·0±11·5	170·9±4·0
	Lower						
	D	0·348±0·003	0·287±0·018	0·272±0·003	0·273±0·009	0·238±0·006	0·215±0·005
	HV	76·14±1·2	112·4±12·8	122·7±3·4	122·3±9·1	161·2±8·1	195·4±9·2
Cellactose	Upper						
	D	—	0·382±0·008	0·309±0·010	0·227±0·010	0·246±0·009	0·217±0·010
	HV	—	62·62±2·8	96·82±7·9	178·9±23·4	152·4±13·9	195·8±24·8
	Lower						
	D	—	0·390±0·005	0·304±0·007	0·236±0·011	0·246±0·012	0·248±0·022
	HV	—	59·97±1·9	98·39±4·7	163·0±16·1	152·0±17·6	159·5±28·1
Tablettose	Upper						
	D	0·277±0·008	0·240±0·006	0·224±0·002	0·222±0·001	0·183±0·005	0·171±0·008
	HV	118·5±7·3	158·0±7·3	181·5±2·1	184·4±2·4	273·2±17·7	313·4±27·4
	Lower						
	D	0·271±0·021	0·234±0·006	0·231±0·010	0·211±0·015	0·189±0·019	0·169±0·011
	HV	125·2±19·4	166·2±9·6	200·8±19·2	203·7±2·3	262·1±51·4	323·9±33·6

using a Zwick 3212 Hardness Testing Machine. Preliminary tests were performed to select an applied force that ensured a permanent indentation in the tablet surface. The force selected was 4·91 N. Contact time was fixed at 10 s.

Results and Discussion

Table 1 shows indentation diameters and Vickers hardness values (average of three tablets) of the upper and lower surface of different tablet batches of Fast Flo Lactose, Ludipress, Cellactose and Tablettose. As expected, the diameter of the indentations decreases and Vickers hardness increases as applied pressure was increased (from batches 1 to 6). For all materials there was no correlation between the Vickers hardness of the upper and lower surfaces.

Fig. 1 represents differences and confidence limits between the Vickers hardness of the upper and lower compact surfaces for Fast Flo Lactose, Ludipress, Cellactose and Tablettose. The highest absolute difference (average of all the batches of each excipient) was exhibited by Tablettose (1·276) and Cellactose (1·158), whereas Fast Flo Lactose and Ludipress showed lower values (0·743 and 0·745, respectively).

Table 2 shows values of tensile strength and Vickers hardness of tablet batches at different pressures. All excipients presented a good linear relationship over the compaction pressure range used (linear correlation coefficient: 0·9833, 0·9829, 0·9445 and 0·9846, respectively, n = 6). This is similar to the linear relationships found by Romano & Vázquez (1988).

Table 3 shows tablet batch parameters of all the excipients studied to evaluate characteristic equations of the consolidation mechanisms.
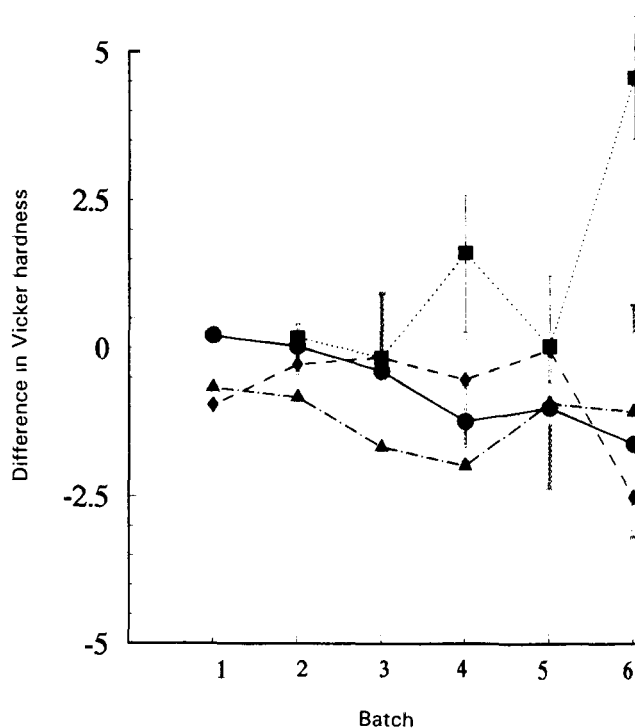

FIG 1. Differences of Vickers hardness between upper and lower surfaces. ● Fast Flo Lactose, ◆ Ludipress, ■ Cellactose, ▲ Tablettose.

A nonlinear regression analysis of experimental data was performed using BMDP statistical software (Department of Biomathematics, University of California, Los Angeles, USA); all the excipients gave non-convergence values of

Table 2. Tensile strength (TS in MPa) and Vickers hardness (HV in MPa) of tablets prepared from a range of lactose-based excipients at different pressures.

Excipient	Batch number					
	1	2	3	4	5	6
Fast Flo Lactose						
HV	19·6±16·0	70·16±12·5	92·6±4·2	130·6±11·6	147·7±10·9	196·2±19·8
TS	0·98±0·008	1·33±0·009	1·84±0·013	1·96±0·009	2·21±0·18	2·90±0·21
Ludipress						
HV	71·54±8·1	111·1±6·0	122·0±3·0	119·5±3·0	161·1±11·5	183·1±4·0
TS	0·83±0·005	1·25±0·012	1·70±0·013	1·81±0·009	2·41±0·021	3·05±0·010
Cellactose						
HV	—	61·74±2·8	97·60±7·9	171·0±23·4	152·2±13·9	173·3±24·8
TS	0·75±0·005	1·36±0·011	1·85±0·014	3·52±0·036	4·14±0·021	—
Tablettose						
HV	121·9±7·3	162·1±7·3	181·5±2·1	184·4±2·4	267·7±17·7	348·0±27·4
TS	0·88±0·003	1·36±0·011	1·83±0·015	1·55±0·009	3·40±0·025	4·74±0·026

Table 3. Parameters of excipients to evaluate characteristic equations of consolidation mechanisms: applied pressure (P_a), thickness (H), apparent density (D_a), relative density (D_r), Vickers hardness (HV) and $\ln 1/(1-D_r)$.

Excipient	P_a (MPa)	H (mm)	D_a (g cm^{-3})	D_r (g cm^{-3})	P_aD_r	HV (MPa)	$\ln(1/(1-D_r))$
Fast Flo	108·21	2·75	1·2722	0·8576	92·815	10·47	1·949
Lactose	142·98	2·67	1·3104	0·8833	126·31	38·02	2·148
	180·26	2·61	1·3405	0·9036	162·91	49·70	2·340
	218·43	2·52	1·3884	0·9359	204·44	66·72	2·784
	228·89	2·52	1·3884	0·9359	214·24	76·55	2·784
	279·18	2·45	1·4280	0·9626	268·76	101·24	3·288
Ludipress	75·120	2·61	1·2061	0·8210	63·649	35·60	1·720
	98·780	2·55	1·2345	0·8403	85·666	58·67	1·834
	126·57	2·51	1·2541	0·8537	111·51	64·79	1·922
	139·44	2·44	1·2901	0·8782	126·38	62·50	2·105
	171·09	2·36	1·3339	0·9079	160·32	86·51	2·385
	213·08	2·31	1·3627	0·9276	203·99	91·04	2·625
Cellactose	60·151	2·82	1·0313	0·6334	38·100	—	1·003
	84·529	2·40	1·2118	0·7442	62·911	33·58	1·363
	111·47	2·44	1·1920	0·7320	81·602	51·32	1·316
	216·54	2·10	1·3850	0·8505	184·18	95·09	1·901
	277·67	2·01	1·4470	0·8886	246·76	80·97	2·195
	298·32	2·02	1·4398	0·8842	263·79	104·1	2·156
Tablettose	136·30	2·39	1·3493	0·8839	120·48	63·86	2·153
	186·73	2·37	1·3607	0·8913	166·44	85·07	2·219
	250·17	2·31	1·3961	0·9145	228·78	97·65	2·459
	252·44	2·32	1·3900	0·9105	229·85	99·42	2·414
	404·08	2·23	1·4462	0·9473	382·80	146·30	2·943
	558·78	2·15	1·5000	0·9825	549·05	167·60	4·050

Leuenberger parameters (compressibility and compactability), in equation 1:

$$P = P_{max}(1 - e^{-\gamma\sigma_c\rho_r}) \tag{1}$$

where P is the deformation resistance or Brinell hardness, P_{max} is the compactability, γ is the compressibility, σ_c is the compression stress and ρ_r is the relative density.

By rearrangement of this equation and by substituting Brinell by Vickers hardness and using the same terms that are used in the Heckel method (1961a, b), equation 2 is obtained:

$$\ln\left(1 - \frac{HV}{HV_{max}}\right) = \gamma\, P_aD_r \tag{2}$$

where HV is the deformation resistance or Vickers Hardness, HV_{max} is the compactability, P_a is the applied pressure or compression stress to make the tablet and D_r is the relative density.

This equation allows a logarithmic-regression adjustment. To calculate the compressibility parameter (γ) using this method, a maximum HV was obtained for each excipient using high applied pressure around 520·4 MPa (maximum performance of eccentric press). Also, deformation resistance is substituted by a relative value of this parameter, i.e. the HV/HV_{max} ratio, where HV_{max} is Vickers hardness of the tablet at maximum applied force.

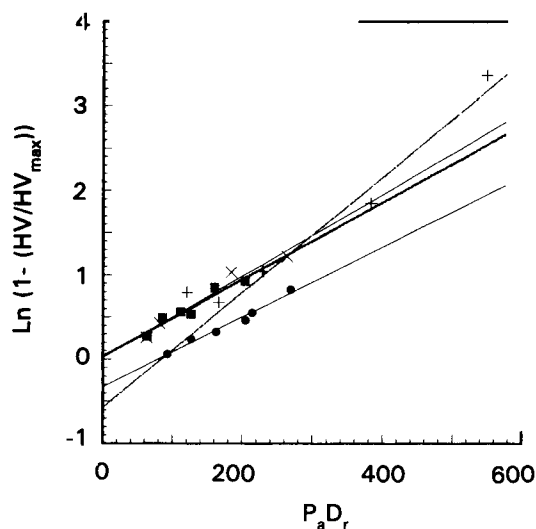Fig. 2 illustrates the relationship between the product P_aD_r

FIG. 2. Fitted plot (continuous line) of experimental points to equation 2. ● Fast Flo Lactose, ■ Ludipress, × Cellactose, + Tablettose.
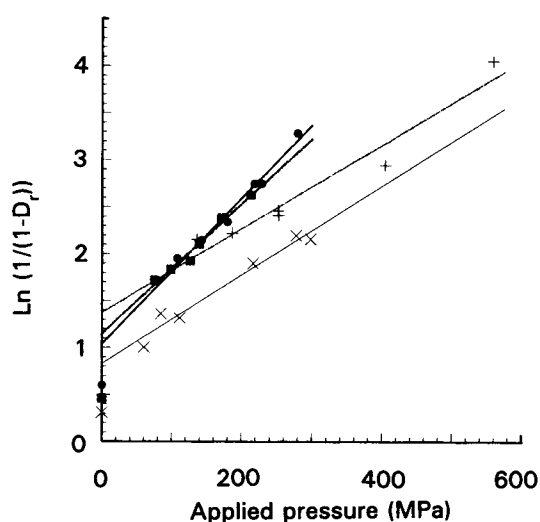

FIG. 3. Ejected-tablet Heckel plots. ● Fast Flo Lactose, ■ Ludipress, × Cellactose, + Tablettose.

and ln $(1 - HV/HV_{max})$ for Fast Flo Lactose, Ludipress, Cellactose and Tablettose.

Heckel plots using the ejected-tablet method are represented in Fig. 3. Fig. 4 represents Heckel plots using the tablet-in-die method.

Lactose-based excipients showed a linear relationship over the range of the product P_aD_r used in this work (Fig. 2). Moreover, these excipients revealed an excellent fit to equation 2 with correlation coefficients between 0·9607 for Ludipress and 0·9905 for Fast Flo Lactose (Table 4). A linear relationship between ln $(1(1-D_r))$ and applied pressure for the ejected-tablet and tablet-in-die methods is observed, giving values of correlation coefficient higher than 0·9749 (Table 5).

Results derived using the Heckel equation and Heckel plots for the ejected-tablet method are shown in Table 5.

Values of compressibility (γ) can be ranked from maxi-

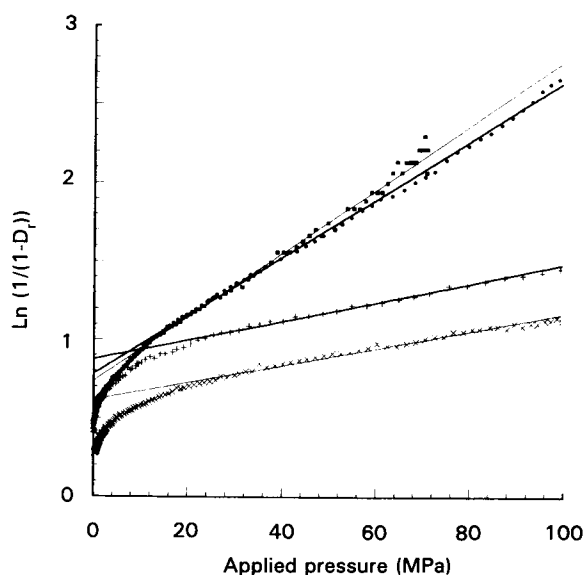FIG. 4. Tablet-in-die Heckel plots. ● Fast Flo Lactose, ■ Ludipress, × Cellactose, + Tablettose.

mum to minimum in the following order: Tablettose, Cellactose, Ludipress and Fast Flo Lactose. This sequence agreed with observed values of yield pressure (P_y) obtained using ejected-tablet and tablet-in-die Heckel methods. In the last case Fast Flo Lactose shows scarcely higher P_y values than Ludipress. This may be explained according to the relative high P_y standard deviation of Ludipress ($\pm 10\cdot6$). Values of P_y obtained using the ejected-tablet method were higher than those calculated by the tablet-in-die method. This is due to the expansion of the tablet after ejection (Paronen 1986). Furthermore, density contribution to movement and rearrangement values, D_b (tablet-in-die method), showed the same tendency for both parameters mentioned. Ludipress exhibited the highest D_b value (ejected-tablet method). This is due to the fact that the density of powder beds (before the applied pressure) depends on the particle size and shape distribution (Doelker 1988); in the case of Ludipress this distribution showed a good fit to a Rosin-Rammler distribution with a high $R_{36\cdot8}$ value (Muñoz-Ruiz et al 1992).

The order of magnitude of P_y values (Table 5) in all cases, demonstrated that these materials are likely to consolidate mainly by brittle fracture.

In contrast, values of HV_{max}, which represent the maximum hardness which would be attained at infinite applied pressure, were very similar for the lactose-based excipients under study, from 147·92 MPa for Cellactose to 179·98 MPa for Fast Flo Lactose (Table 4). However, high values of this parameter ($> 10^2$) verified their consolidation mechanisms by brittle fracture (Jetzer 1986), corroborated by compressibility values of $< 10^{-2}$. Whilst HV for solids which undergo plastic deformation approach HV_{max}, even at low applied pressure.

The fragmentation propensity of the substances, based on parameters cited above, was (from maximum to minimum): Tablettose, Cellactose, Ludipress and Fast Flo Lactose. The values of the parameters accepted as a determinant of the consolidation mechanisms (compressibility, P_y, D_b) showed

Table 4. Values of compactability (HV_{max} in MPa) and compressibility (γ in MPa^{-1}), correlation coefficient (r), values of F-tests (F) and probability level (P).

Excipient	HV_{max}	γ	r	F	P
Fast Flo Lactose	$179\cdot98 \pm 2\cdot31$	$0\cdot00438 \pm 0\cdot0004$	$0\cdot9905$	$207\cdot53$	$>0\cdot999$
Ludipress	$151\cdot23 \pm 1\cdot10$	$0\cdot00456 \pm 0\cdot0006$	$0\cdot9607$	$47\cdot91$	$>0\cdot999$
Cellactose	$147\cdot92 \pm 0\cdot90$	$0\cdot00483 \pm 0\cdot0006$	$0\cdot9804$	$74\cdot28$	$>0\cdot999$
Tablettose	$173\cdot61 \pm 2\cdot19$	$0\cdot00683 \pm 0\cdot0007$	$0\cdot9759$	$59\cdot79$	$>0\cdot999$

Table 5. Results derived using Heckel tablet-in-die and ejected-tablet methods from experimental data obtained: intercept density of the linear regression (D_a), density contribution to movement and rearrangement (D_b), relative density of precompression (D_0), yield pressure (P_y), correlation coefficient (r) and values of F-tests (F).

Excipient	Method	D_a (g cm^{-3})	D_b (g cm^{-3})	D_0 (g cm^{-3})	P_y (MPa)	n	r	F
Fast Flo Lactose	Tablet ejected	$0\cdot645 \pm 0\cdot021$	$0\cdot195 \pm 0\cdot019$	$0\cdot450 \pm 0\cdot002$	$128\cdot6 \pm 9\cdot6$	6	$0\cdot9889$	$177\cdot2$
	Tablet-in-die	$0\cdot535 \pm 0\cdot023$	$0\cdot162 \pm 0\cdot019$	$0\cdot373 \pm 0\cdot002$	$52\cdot06 \pm 6\cdot4$	73	$0\cdot9972$	5248
Ludipress	Tablet ejected	$0\cdot684 \pm 0\cdot016$	$0\cdot316 \pm 0\cdot025$	$0\cdot367 \pm 0\cdot009$	$144\cdot9 \pm 14\cdot3$	6	$0\cdot9889$	$146\cdot3$
	Tablet-in-die	$0\cdot496 \pm 0\cdot018$	$0\cdot226 \pm 0\cdot023$	$0\cdot360 \pm 0\cdot006$	$48\cdot2 \pm 10\cdot6$	85	$0\cdot9972$	7327
Cellactose	Tablet ejected	$0\cdot563 \pm 0\cdot018$	$0\cdot299 \pm 0\cdot023$	$0\cdot265 \pm 0\cdot006$	$211\cdot4 \pm 10\cdot6$	5	$0\cdot9820$	$108\cdot1$
	Tablet-in-die	$0\cdot465 \pm 0\cdot009$	$0\cdot226 \pm 0\cdot008$	$0\cdot239 \pm 0\cdot002$	$182\cdot7 \pm 17\cdot7$	65	$0\cdot9950$	5729
Tablettose	Tablet ejected	$0\cdot747 \pm 0\cdot018$	$0\cdot333 \pm 0\cdot017$	$0\cdot415 \pm 0\cdot001$	$224\cdot3 \pm 6\cdot60$	6	$0\cdot9749$	$76\cdot7$
	Tablet-in-die	$0\cdot599 \pm 0\cdot018$	$0\cdot256 \pm 0\cdot017$	$0\cdot333 \pm 0\cdot001$	$203\cdot2 \pm 6\cdot6$	71	$0\cdot9895$	3103

good agreement with the series of absolute values of differences between upper and lower surfaces of the tablet. These results indicated the possibility of using the difference between upper and lower surface hardness of the tablets made on an eccentric press to determine the comparative consolidation mechanisms of different substances.

Recently, a combination of the Heckel equation with the Leuenberger equation was applied to the formation of tablets based on the percolation theory (Leu & Leuenberger 1992).

References

Aulton, M. E. (1981) Indentation hardness profile across the face of some compressed tablets. Pharm. Acta Helv. 56: 133–137

Doelker, E. (1988) Recent advances in tableting science. Boll. Chim. Farm. 127: 37–49

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

Heckel, R. W. (1961a) Density-pressure relationship in powder compaction. Trans. Metall. Soc. AIME 221: 671–675

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

Hersey, J., Rees, J. (1973) Density changes in lactose tablets. J. Pharm. Sci. 62: 2060

Humbert-Droz, P., Mordier, D., Doelker, E. (1982) Methode rapide de détermination du comportament à la compression pour études de préformulation. Pharm. Acta Helv. 57: 136–143

Jetzer, W., Leuenberger, H., Sucker, H. (1983) The compressibility

and compactability of pharmaceutical powders. Pharm. Technol. 11: 33–39

Jetzer, W. E. (1986) Measurement of hardness and strength of tablets and their relation to compaction performance of powders. J. Pharm. Pharmacol. 38: 254–258

Leu, R., Leuenberger, H. (1992) The application of the percolation theory to the formation of a tablet. 6th International Conference on Pharmaceutical Technology. Paris, June 1992, Vol I, pp 402–409

Leuenberger, H. (1982) The compressibility and compactability of powder systems. Int. J. Pharm. 12: 41–55

Muñoz-Ruiz, A. (1992) Diseño de Sistemas de Adquisición y Tratamiento de Datos Para Velocidades de Flujo de Polvos y Estudio de Compresión en Máquina de Comprimir Excéntrica. Aplicación en Excipientes de Compresión Directa. Doctoral Thesis, Universidad de Sevilla

Muñoz-Ruiz, A., Borrero, J. M., García, M. A., Jiménez-Castellanos, M. R., Faulí, C. (1988) Un programa de ordenador para el estudio reológico de los polvos. Ciencia e Industria Farmacéutica 7: 321–325

Münoz-Ruiz, A., Borrero, J. M., Jiménez-Castellanos, M. R. (1992) Ludipress a new excipient for direct compression. Pharm. Acta Helv. 67: 223–226

Paronen, P. (1986) Heckel plots as indicator of elastic properties of pharmaceuticals. Drug Dev. Ind. Pharm. 12: 1903–1912

Ridgway, K., Aulton, M. E., Rosser, P. H. (1970) The surface hardness of tablets. J. Pharm. Pharmacol. 22 (Suppl.): 70S–78S

Romano, S., Vázquez, F. (1988) Determinación de la resistencia mecánica de comprimidos II. Estudio en comprimidos de excipientes para compresión directa. Ciencia e Industria Farmacéutica 7: 241–246

Westbrook, J. H., Conrad, H. (1973) The Science of Hardness Testing and its Research Applications. American Society for Metals, Metals Park, Ohio