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ANALYSIS COMPARATIVE OF METHODS TO EVALUATE CONSOLIDATION MECHANISMS IN PLASTIC AND VISCOELASTIC MATERIALS USED AS DIRECT COMPRESSION EXCIPIENTS

M. C. Monedero Perales, A. Muñoz Ruiz, M. V. Velasco Antequera, N. Muñoz Muñoz and M. R. Jiménez-Castellanos.

Departamento de Farmacia y Tecnología Farmacéutica.
Facultad de Farmacia. c/ Tramontana s/n Sevilla 41012. SPAIN.

SUMMARY

In order to better explain the mechanisms of tablet formation, there is now a greater tendency to investigate particle deformation rather than bulk deformation of the powder bed.

In this sense, measurements of static indentation in tablet to determine compressibility and compactability of powders were used. In this work this method, using as hardness testing a pyramid instead of a ball into the surface of the tablet under test, is compared to Heckel plots using ejected tablet method. Also, bonding index, absolute differences between indentation hardness of tablet surfaces and force-displacement curves were used to establish behaviour of excipients that undergo compression deform plastically and viscoelastic excipients with tendency to deform plastically until applied pressure was exceeded.

INTRODUCTION

A knowledge of the mechanical properties is an important aspect of the control of pharmaceutical tablets and the investigation of tensile strength and indentation hardness provides useful information into the process of compaction and therefore in the formulation of the tablet (1-3).

In the measurement of mechanical strenght various techniques have been used including (4): Static indentation , Scratch , Plowing , Rebound , Damping , Cutting , Abrasion , Erosion and Tablet tensile strength tests.

Brinell hardness in tablets was used to obtain results independent of tablet geometry (5), as well as, tensile failure along the vertical center-line produced by diametral compression (1,6). In this sense, the measurements of static indentation in tablet were used to determine compressibility and compactability of powders (5). Also, the relation between the two mechanical properties -tensile strength and indentation hardness- was investigated (3).

The goal of this study is to measure the indentation hardness, using as hardness testing a pyramid (Vickers hardness) instead of a ball into the surface of the tablet under test and to compare with Heckel plots using ejected tablet method (7,8,9). Furthermore, the ratio between tensile strength and indentation hardness (10) is calculated with the purpose of using these compaction parameter to predict tableting behaviour of the excipients under study.

Materials tested were excipients that undergo compression deform plastically and viscoelastic excipients with tendency to deform plastically (11) until applied pressure was exceeded (12).

MATERIAL AND METHODS

In this study four excipients for direct compression were used; Avicel® PH 101 -batch 1931-, Avicel® PH 200 -batch 2947- (FMC Corp., Philadelphia, USA), Starch Rx

1500® -batch 910453- (Dr. Esteve, Barcelona, Spain) and Sepistab® St 200 -batch 3710- (SEPPIC, Paris, France).

Compression characteristics of the powders were investigated on an instrumented single punch tablet machine (Bonals AMT 300, Barcelona, Spain) with strain gauges HBM YL6 with dynamic amplifiers (NEC San-ei, Tokyo, Japan) and inductive displacement transducers (HBM, Darmstat, Germany), and A/D Converter Metrabyte DAS 16G1 (METRABYTE, Ma, USA). A quantity of powder to produce tablets of thickness at zero theoretical porosity was separately weighted and manually filled into the die (12 mm). Flats compacts were prepared at seven different pressures. Tablets were made after lubricating the die with a chloroformic solution of magnesium stearate (5% w/v). Tablet press was running at 30 cycles/minute.

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

The Vickers hardness of each batch is the average of three tablets. Diameters of the indentation were measured using a Zwick 3212 Hardness Testing Machine.

RESULTS AND DISCUSSION

Table 1 shows indentation diameters and Vickers hardness (average three tablets) of upper and lower surface for different tablet batches of Avicel® PH 101, 200, Starch Rx® 1500 and Sepistab®.

Different tests were performed in order to select adequate applied force to obtain measurement of indentation left in the tablet surface. Force selected was 4.91 N (0.5 Kp). Contact time was fixed at 10 seconds. As expected, diameters of the indentation

TABLE 1.- *Average of diameters (D) and Vickers hardness (HV) of upper and lower surfaces of tablets.*

Excipient	Surface		# Batch 1	2	3	4	5	6
Avicel® PH 101	Upper	D	0.572 ± .010	0.444 ± .021	0.398 ± .020	0.340 ± .006	0.328 ± .003	0.276 ± .009
		HV	1.12 ± 0.06	1.89 + 0.17	2.31 ± 0.21	3.20 + 0.22	3.45 ± 0.08	4.87 + 0.36
	Lower	D	0.561 ± .018	0.436 + .017	0.409 ± .012	0.328 ± .002	0.316 ± .001	0.254 ± .006
		HV	1.17 ± 0.07	1.94 ± 0.14	2.21 ± 0.15	3.43 + 0.04	3.68 ± 0.01	5.62 + 0.42
Avicel® PH 200	Upper	D	0.858 ± .019	0.406 ± .001	0.329 + .010	0.281 ± .006	0.263 ± .001	.236 + .008
		HV	0.50 ± 0.02	2.26 ± 0.01	3.51 + 0.40	4.68 + 0.22	5.36 + 0.06	6.65 + 0.40
	Lower	D	0.898 ± .016	0.392 ± .011	0.354 ± .023	0.256 ± .002	0.259 ± .012	0.230 ± .003
		HV	0.45 + 0.01	2.41 ± 0.13	2.98 ± 0.41	5.28 + 0.11	5.60 + 0.58	6.99 + 0.23
StaRx® 1500	Upper	D	0.661 ± .070	0.793 ± .070	0.817 ± .005	0.247 + .007	0.243 ± .006	0.178 + .008
		HV	2.25 ± 0.47	1.54 ± 0.23	1.42 ± 0.03	15.26 ± 0.93	15.79 ± 0.79	29.30 ± 2.75
	Lower	D	0.715 ± .029	0.772 ± .030	0.788 ± .046	0.256 ± .011	0.246 ± .007	0.164 ± .001
		HV	1.37 ± 0.92	1.56 ± 0.12	1.51 ± 0.18	14.13 ± 1.26	15.34 ± 0.83	34.14 + 0.62
Sepis-tab® St 200	Upper	D	0.532 ± .010	0.452 ± .020	0.352 ± .002	0.326 ± .008	0.251 ± .010	0.232 ± .000
		HV	6.56 ± 0.38	9.15 + 0.89	14.98 ± 0.15	17.55 ± 0.88	29.72 ± 2.94	34.54 ± 0.09
	Lower	D	0.549 + .003	0.437 ± .005	0.351 ± .007	0.326 + .007	0.245 ± .012	0.226 ± .001
		HV	6.15 ± 0.08	9.72 ± 0.24	15.08 + 0.59	17.48 + 0.80	30.98 ± 3.26	36.25 ± 0.42

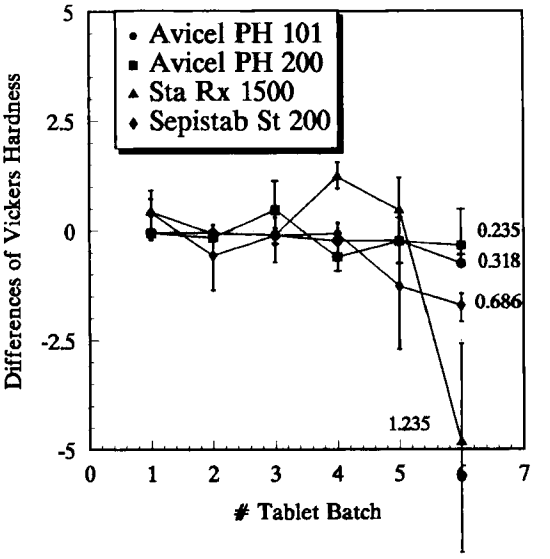

FIGURE 1
Differences of VICKERS hardness between upper and lower surfaces

decreases and Vickers hardness increases as applied pressure was increased from 1st to 6th batch, excepting in Starch Rx® 1500 which shows non statistical difference between the three first batches.

For all materials there was not any relationship between Vickers hardness of upper and lower surfaces.

Figure 1 represents differences and confidence limits between Vickers hardness of upper and lower surfaces for Avicel® PH 101, 200, Starch Rx® 1500 and Sepistab®. Microcrystalline celluloses (Avicel® PH 101 and 200) exhibit the lowest absolute values, whereas Starch Rx® 1500 and Sepistab® show higher values than microcrystalline celluloses. Low values of differences between Vickers hardness of upper and lower surfaces suggest an intrinsic high tendency to plastic deformation, as occurs in Avicel® PH 101 and 200. Furthermore, the cellulose (13) particles exhibit a composite structure of smaller elongated particles or fibrils, and undergo extensive deformation during compaction. On the opposite, in the case of a viscoelastic material, as modified starch (14) showed higher values. In this last case, Starch Rx® 1500 shows higher average of absolute differences (1.235) than Sepistab® (0.686).

TABLE 2.- Values of tensile strength (TS) and Vickers hardness (HV) of tablet batches at different pressures.

# Batch		1	2	3	4	5	6
Avicel® PH 101	HV	1.15 ± .01	1.92 ± .17	2.26 ± .31	3.32 ± .22	3.57 ± .08	5.25 ± .36
	TS	0.599 ± .06	1.035 ± .09	1.453 ± .16	1.876 ± .19	2.367 ± .20	3.413 ± .29
Avicel® PH 200	HV	0.48 ± .02	2.34 ± .01	3.25 ± .40	4.98 ± .22	5.48 ± .06	6.82 ± .40
	TS	0.570 ± .05	0.946± .10	1.361 ± .15	2.311 ± .19	2.394 ± .21	3.120 ± .11
Sta Rx 1500®	HV	1.81 ± .47	1.55 ± .23	1.47 ± .03	14.70 ± .93	15.57 ± .79	31.92 ± 2.75
	TS	0.743 ± .08	1.150± .09	1.654 ± .11	1.367 ± .09	1.456 ± .10	1.560 ± .15
Sepistab® St 200	HV	6.36 ± .38	9.44 ± .89	15.03 ± .15	17.52 ± .88	30.35 ±2.94	35.40 ± .09
	TS	0.711 ± .06	1.176± .12	1.577 ± .18	1.544 ± .12	1.597 ± .17	1.379 ± .12

Table 2 shows values of tensile strength and Vickers hardness of tablet batches at different pressures.

ROMANO (1) found a linear relationship between tensile strength and Vickers hardness. In this way, Avicel® PH 101 and 200 show a linear relationship over the compaction pressure range used (linear correlation coefficient: 0.9938 and 0.9895 respectively). In contrast, Starch Rx® 1500 and Sepistab® exhibit a non-linear relation (linear correlation coefficient: 0.4535 and 0.5393 respectively).

This fact indicates that a significant factor in the type of relation between both parameters is the mechanical properties of the materials. In this sense, it is important for practical purposes to know enough about the mechanisms of compaction and consolidation of the powders to be able to obtain a tablet of adequate mechanical properties, selecting every time adequate technique to measure mechanical strength.

TABLE 3.- *Parameters of* ***Avicel® PH 101*** *to evaluate characteristic equations of consolidation mechanism: applied pressure (Pa), thickness (H), apparent density (Da), relative density (Dr), Vickers hardness (HV) and Ln 1/1-Dr.*

# Batch	Pa (MPa)	H (cm)	Da (g/cm^3)	Dr (g/cm^3)	Pa*Dr	HV (MPa)	Ln 1/(1-Dr)
1	17.040	0.345	0.8405	0.5547	9.452	7.064	0.809
2	20.951	0.310	0.9354	0.6173	12.934	9.952	0.960
3	28.883	0.292	0.9914	0.6542	18.897	12.386	1.062
4	37.543	0.290	0.9999	0.6599	24.775	16.972	1.078
5	44.760	0.277	1.0469	0.6908	30.924	18.236	1.174
6	64.302	0.260	1.1153	0.7360	47.330	25.756	1.332

Tables 3-6 show parameters of excipient tablet batches to evaluate characteristic equations of the consolidation mechanisms: applied pressure (Pa), thickness (H), apparent density (Da), relative density (Dr), Vickers hardness (HV) and Ln 1/1-Dr.

A non-linear regression analysis of experimental data was performed with BMDP giving non-convergence values of Leuenberger parameters. Equation 1:

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

where:

- P deformation resistance or Brinell Hardness
- σ_c compression stress
- ρ_r relative density
- P_{max} compactability
- γ compressibility

In this way, by rearrangement of this equation, substituting Brinell by Vickers hardness and using the same terms that in the Heckel method (15, 16) the Equation 2

*TABLE 4.- Parameters of **Avicel® PH 200** to evaluate characteristic equations of consolidation mechanism: applied pressure (Pa), thickness (H), apparent density (Da), relative density (Dr), Vickers hardness (HV) and Ln 1/1-Dr.*

# Batch	Pa (MPa)	H (cm)	Da (g/cm^3)	Dr (g/cm^3)	Pa*Dr	HV (MPa)	Ln 1/(1-Dr)
1	18.930	0.375	0.7756	0.5138	9.727	2.665	0.721
2	24.780	0.337	0.8630	0.5717	14.168	11.902	0.848
3	33.600	0.311	0.9352	0.6195	20.818	18.126	0.966
4	40.580	0.285	1.0205	0.6761	27.436	24.847	1.127
5	47.930	0.282	1.0313	0.6833	32.750	28.365	1.149
6	57.060	0.272	1.0693	0.7084	40.422	35.226	1.231

*TABLE 5.- Parameters of **Sta Rx® 1500** to evaluate characteristic equations of consolidation mechanism: applied pressure (Pa), thickness (H), apparent density (Da), relative density (Dr), Vickers hardness (HV) and Ln 1/1-Dr.*

# Batch	Pa (MPa)	H (cm)	Da (g/cm^3)	Dr (g/cm^3)	Pa*Dr	HV (MPa)	Ln 1/(1-Dr)
1	98.587	0.286	1.1336	0.7625	75.178	11.210	1.437
2	167.05	0.278	1.1662	0.7844	131.05	7.792	1.534
3	190.74	0.253	1.2814	0.8620	164.42	7.341	1.980
4	290.51	0.256	1.2664	0.8519	247.49	80.316	1.909
5	339.50	0.255	1.2714	0.8552	290.36	82.980	1.932
6	447.63	0.256	1.2664	0.8519	381.34	154.70	1.909

TABLE 6.- *Parameters of **Sepistab St 200®** to evaluate characteristic equations of consolidation mechanism: applied pressure (Pa), thickness (H), apparent density (Da), relative density (Dr), Vickers hardness (HV) and Ln 1/1-Dr.*

# Batch	Pa (MPa)	H (cm)	Da (g/cm^3)	Dr (g/cm^3)	Pa*Dr	HV (MPa)	Ln 1/(1-Dr)
1	79.577	0.296	1.0779	0.7361	58.578	34.66	1.332
2	134.94	0.276	1.1560	0.7894	106.53	48.02	1.558
3	211.53	0.269	1.1861	0.8100	171.34	79.17	1.660
4	318.10	0.261	1.2225	0.8348	265.56	92.31	1.800
5	392.26	0.260	1.2272	0.8380	328.73	155.7	1.820
6	474.16	0.260	1.2272	0.8380	397.36	182.3	1.820

is obtained:

$$Ln\left(1 - \frac{HV}{HV_{max}}\right) = \gamma P_a D_r \qquad (2)$$

where:

HV deformation resistance or Vickers Hardness

Pa applied pressure

D_r relative density

HV_{max} compactability

This equation let us do a linear-regression adjustment. In order to calculate the compressibility parameter (γ) using this method, a maximum HV was obtained for each excipient using high applied force around 6 Tons (maximum performance of eccentric press). Also, deformation resistance is substituted by a relative value HV/HV_{max} ratio; where HV_{max} is Vickers Hardness of tablet at maximum applied force.

Figure 2a,b illustrates the relationship between Pa Dr and Ln $(1-HV/HV_{max})$ and the adjustement of experimental points to the modified Leuenberger equation for Avicel® PH 101, 200 (Figure 2a) and for Starch® Rx 1500 and Sepistab® (Figure 2b).

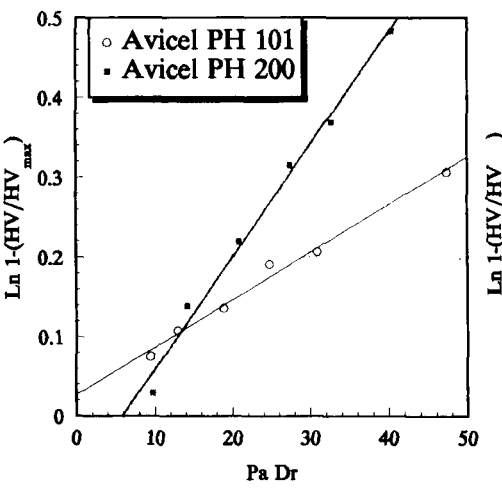

Figure 2a

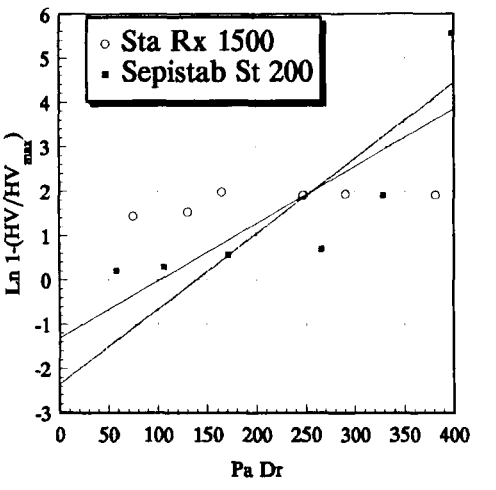

Figure 2b

FIGURE 2
Fitting plots to equation 2

Avicel® PH 101 and 200 showed a linear relationship over the Pa-Dr range used (Figure 2a). Moreover, these excipients revealed excellent fit to equation 2; correlation coefficient of 0.9943 and 0.9947 respectively (Table 7). On the opposite, in Starch Rx® 1500 and Sepistab® the relationship is non-linear (Figure 2b) with correlation coefficients of 0.8049 and 0.8229 respectively (Table 7).

Values of compactability (HV_{max}), which represent the maximum hardness which would be attained to infinite applied pressure, showed higher values in starches than in microcrystalline celluloses. Solids undergo plastic deformation approach to hardness HV_{max} even at low applied pressure (5). In the case of microcrystalline celluloses low values of this parameter $< 10^2$ (Table 7) verified their consolidation mechanics by plastic deformation. However, these values in starches were $> 10^2$ (Table VII) signifying brittle fracture, in spite of their compressibility values $> 10^{-2}$ indicated plastic deformation. Indeed starches with tendency to deform plastically until applied pressure (11, 12) was exceeded gave non-physical significance values of HV_{max}.

Heckel plots using tablet ejected method are represented in Figure 3 a,b for Avicel® PH 101, 200 (Figure 3a) and for Starch Rx® 1500 and Sepistab® (Figure 3b).

TABLE 7.- Values of compactability (HVmax), compressibility (γ), correlation coefficient (r), value of F-tests (F) and probability level (p).

EXCIPIENT	HVmax	γ	r	F	p
Avicel®101	97.66 ± 0.36	0.00597 ± 0.0003	0.9943	347.88	> 0.999
Avicel®200	91.94 ± 0.32	0.01400 ± 0.0007	0.9947	374.36	> 0.999
Sta Rx® 1500	155.00 ± 1.12	0.01697 ± 0.0062	0.8049	7.35	> 0.95
Sepistab®	183.07 ± 2.03	0.01289 ± 0.0044	0.8229	8.39	> 0.95

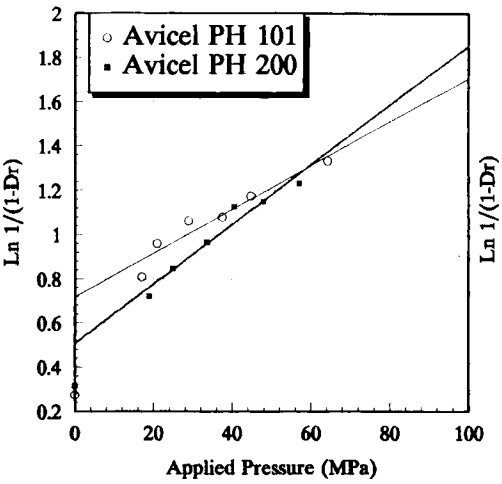

Figure 3a

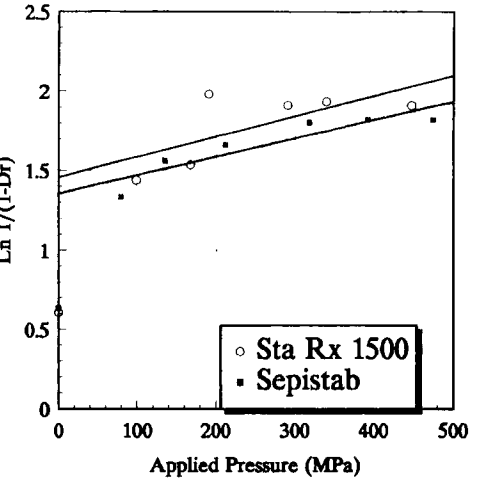

Figure 3b

FIGURE 3
Heckel tablet ejected plots

TABLE 8.- Results derived, using Heckel equation.

Excipient	Py	D_a	D_0	D_b	N	r	F	p
Avicel® PH 101	101.11	0.512	0.2377	0.2743	6	0.9634	51.67	> 0.999
Avicel® PH 200	74.28	0.398	0.2698	0.1282	6	0.9763	81.40	> 0.999
Sta Rx® 1500	781.37	0.767	0.4545	0.3125	6	0.6988	3.82	< 0.90
Sepistab®St 200	863.56	0.742	0.4693	0.2726	6	0.9107	19.44	> 0.99

Results derived, using Heckel equation, from experimental data (Tables 3-6) obtained (N) appear in Table 8: intercept density of the linear regression (Da), density contribution to movement and rearrangement (Db), relative density of precompression (D_0), yield pressure (Py). Also, correlation coefficient (r), values of F-tests for significance of regression (F) and probability level (p).

Avicel® PH 200 exhibited values of Py and D_b lower than Avicel® PH 101, meaning in the first case a more extensive plastic deformation. These results were according to values of parameters obtained using Equation 2, Avicel® PH 200 showed higher value of compressibility (two times higher) and lower value of compactability than PH 101 (Table 7). These results were consistent with LEUENBERGER (17) that found, within experimental error, a proportionality between compressibility (γ) and yield pressure.

The order of magnitude of Py values in the starches is seven times higher than in celluloses (Table 8). This is due to the non linear relationship between Ln (1/1-Dr) and applied pressure giving low values of correlation coefficient 0.6988 in the case of Starch Rx® 1500 and 0.9107 in the other starch Sepistab® St 200 (Table 8).

Starches Sta Rx® 1500 and Sepistab® St 200 demonstrated values of HVmax and compressibility closer to their consolidation mechanism -viscoelastic excipients with tendency to deform plastically (11) until applied pressure was exceeded (12)- than yield pressure and Db obtained from Heckel tablet ejected plot. Moreover, Sepistab® St 200 exhibited best fitting to Heckel plot and Equation 2 than Sta Rx® 1500.

However, to explain the consolidation mechanisms it is evident that one single parameter, index or method is not sufficient to describe the variety of compaction

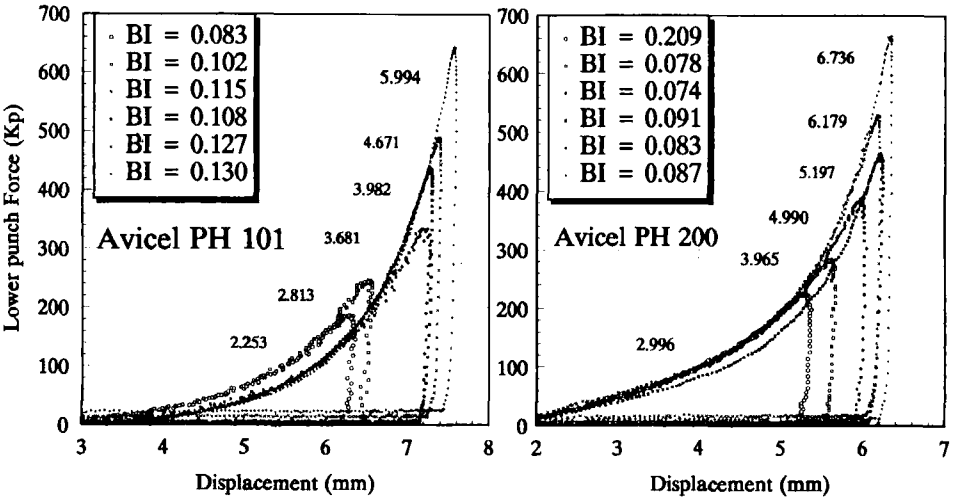

Figure 4a Figure 4b

FIGURE 4

Force-Displacement curves of microcrystalline celluloses (values of areas under curves)

properties that may be incurred. Here it is interesting to calculate the bonding index, ratio between tensile strength and indentation hardness, proposed by HIESTAND (10) for the different batches of all the tablet excipients. These parameters are given in force-displacement curves: Figure 4a,b for Avicel® PH 101 (Figure 4a) and for Avicel® PH 200 (Figure 4b), and also in Figure 5a,b for Starch Rx® 1500 (Figure 5a) and Sepistab® (Figure 5b). Deformation hardness and bonding index (BI) were measured after elastic recovery has taken place (18) instead of using dynamic method which permits calculation of strain index (10).

In these Figure 4 may be observed in both cases, as expected, that area under curve and applied force increase as displacement increases. Although, bonding index showed scarcely differences among the six batches in these microcrystalline celluloses. Only in the first batch of Avicel® PH 200 exhibited a value of 0.2096 higher than the average value of the rest (0.0824) This fact may be justified with the complicated fracture pattern exhibited in this case, confirming that this material predominantly plastic does not purely break in tension. In this sense, it has been shown that to obtain reproducible results for strength, the compacts must break in such a manner that tensile stress were

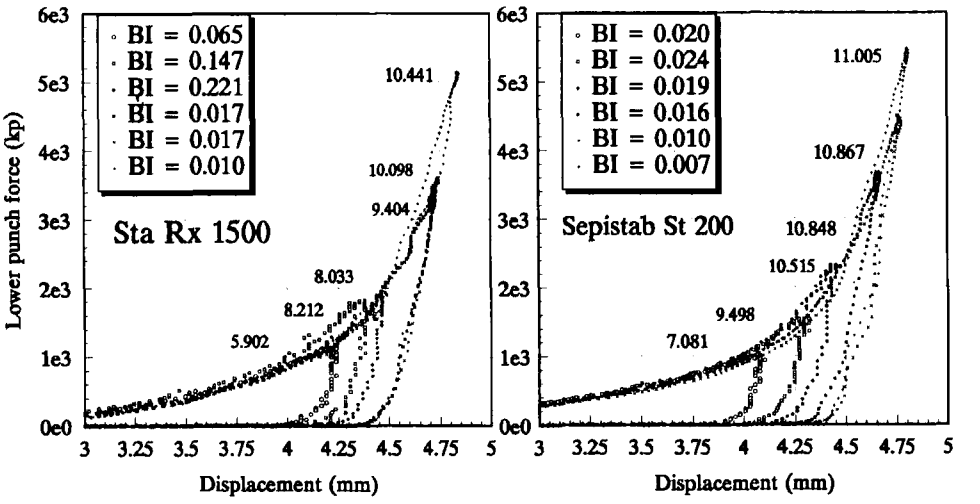

Figure 5a Figure 5b

FIGURE 5

Force-Displacement curves of starches (and values of areas under curves)

the major stress (2). Measurement of tensile strength in low values for this material is probably out of the range of comparability and applicability of this test (3).

Figure 5 displays the elastic recovery during decompression of starches higher than observed for microcrystalline celluloses. In the Figure 5b may be observed, that area under curve and applied force increase as displacement increases. Although, bonding index showed scarce decrease as displacement and force increase. Additionally, the form of the curves demonstrated the proximity of the zones corresponding to compression and decompression in curves #4-6 at highest forces. Nevertheless, data of compression and decompression were superimposed establishing the low capacity to deform plastically at the highest applied pressures.

Figure 5a displays clear differences between the three first F-D curves and the other curves. These differences are consistent with the values of bonding index that showed in batches #4-6, values 0.017-0.010 seven times lower that values of batches #1-3. Furthermore, the form of the curves demonstrated the proximity of the zones corresponding to compression and decompression in curves #4-6 at highest forces. Besides, data of compression and decompression were superimposed establishing the incapacity to deform plastically at the highest applied pressures.

The average bonding index of the excipients were: Avicel® PH 101 (0.1160), Avicel® PH 200 (0.0824), Starch Rx 1500® (0.0791) and Sepistab St 200® (0.0161). Values obtained for microcrystalline celluloses were higher than for starches, due to the highest viscoelasticity of starches. This sequence shows a good agreement with the series of absolute values of differences between upper and lower surface tablet (average computing all batches of each excipients).

However, the dissimilarity between the bonding index of Starch Rx 1500® (0.0791) and Sepistab St 200® (0.0161) may be explained with the difference observed in values of bonding index that showed in batches #4-6 of Sta Rx® values 0.017-0.010 seven times lower that values of batches #1-3. This factor confirms the drastic variation in the mechanical properties of this Starch with the applied pressure.

CONCLUSIONS

The microcrystalline cellulose under study exhibited an excellent fit to equation proposed in this paper. In this way their correlation coefficient showed a linear relationship between Ln (1-HV/HV_{max}) over the Pa Dr range. Consolidation mechanism, as expected, was mainly by plastic deformation. Quantitative data on consolidation process (compressibility, HV_{max}, yield pressure and Db) showed higher plastic deformation in the new Avicel® PH 200 than in Avicel® PH 101.

In starch-based excipients it is evident that one single parameter, index or method is not sufficient to describe the variety of compaction properties that may be incurred. To explain the consolidation mechanisms in Sta Rx® 1500 and Sepistab® St 200 indentation hardness and therefore values of HVmax and compressibility demonstrated more relevance than yield pressure and Db obtained from Heckel tablet ejected plot. Moreover, Sepistab® St 200 exhibited best fitting to Heckel plot and Equation 2 and also more predictable mechanical properties (bonding index, F-D curves) than Sta Rx® 1500.

The absolute value of the difference between upper and lower hardness surfaces of the tablets made on eccentric press may be utilize to establish the comparative consolidation mechanics of different substances.

REFERENCES

1.- S. Romano and F. Vázquez, C.I.F., 7, 241 (1988).

2.- J.T. Fell and J.M. Newton, J. Pharm. Sci., 59, 688 (1970).

3.- W. E. Jetzer, J. Pharm. Pharmacol., 38, 254 (1986).

4.- J.H. Westbrook and H. Conrad in "The science of hardness testing and its research applications", American Society for Metals, Metals Park, Ohio, 1973.

5.- H. Leuenberger, W. Jetzer and H. Sucker, Pharm. Technol., 11, 33 (1983).

6.- P. Rigdway: "Tablet machine instrumentation in pharmaceutics. Principles and practice." Ellis Horwood series in Pharmaceutical Technology. Toronto. 1988.

7.- P. Paronen, Drug Dev. & Ind. Pharm., 12, 1903 (1986).

8.- J.T. Fell and J.M. Newton, J. Pharm. Sci., 60, 1866 (1971).

9.- J. Hersey and J. Rees, J. Pharm. Sci., 62, 2060 (1973).

10.- E.N. Hiestand and D.P. Smith, Powder Technology, 38, 145 (1985).

11.- P. Humbert-Droz, D. Mordier and E. Doelker, Pharm. Acta Helv., 57, 136 (1982).

12.- D. Travers and M. Cox, Drug Dev. & Ind. Pharm., 4, 157 (1968).

13.- Tsardaka, K.D. and Rees, J.E., 6th International Conference on Pharmaceutical Technology, Paris, 1992. Vol IV pp. 169-178.

14.- Rees, J.E. and Malamataris, S., 6th International Conference on Pharmaceutical Technology, Paris, 1992. Vol IV pp. 179-188.

15.- R. W. Heckel, Trans. Metall. Soc. AIME, 221, 671 (1961).

16.- R. W. Heckel, Trans. Metall. Soc. AIME, 221, 1001 (1961).

17.- H. Leuenberger, and W. Jetzer, Powder Technology, 37, 209 (1984).

18.- M. Aulton, Manuf. Chem. Aerosol news, 48, 28 (1977).