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PRELIMINARY INVESTIGATIONS ON THE PARITY OF TABLET COMPRESSION DATA OBTAINED FROM DIFFERENT INSTRUMENTED TABLET PRESSES

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INTRODUCTION

For many years, the formulation, development and manufacture of pharmaceutical tablets have been segregated processes. In the last few years, there has been an increasing interest in obtaining a comprehensive understanding of the nature of interparticulate interactions of pharmaceutical powders being compacted (1). Recently, several workers have addressed the differences between the single station eccentric machine and the multi-station rotary tablet machine (2). The physical differences observed between tablets produced on the two types of machines have been largely attributed to diffences in the punch dwell time during the compaction process. The basis for understanding the physio-mechanical behavior of powders under various compaction environ-

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ments may be provided by the development and use of computerized tablet machine simulators.

This paper reports on the preliminary stages of a study designed to compare the compaction of several direct compression matrices on different rotary tablet machines. It is hoped that an understanding on the degree of parity of the data obtained from the different rotary tablet machines can be gained, and allow a meaningful comparison to be made of the material compaction properties on the three types of machines.

MATERIALS

Direct compression matrices consisting of Avicel PH-101[1] and Emcompress[2] were used. Each matrix was blended for five minutes in a WAB Turbula Type T2C shaker/mixer with an amount of magnesium stearate which would result in a 0.5 %w/w concentration of lubricant in the final blend. These materials were then stored for twenty-four hours in polyethylene bags before being compressed.

METHODS

Three rotary tablet presses were chosen that would represent the kinds of tablet presses used most often in a pharmaceutical development laboratory. These consisted of: a Stokes B-2 sixteen station Rotary Tablet Press, a Manesty B3B sixteen station Rotary Tablet Press and a Colton Model 204 four station Rotary Tablet Press. Each of the presses were operated with tooling in four of the stations, and blank dies were placed in the remaining stations on the Stokes and Manesty presses. All the tablet presses were run at an operational speed of forty revolutions per minute.

The tablet presses differ in the method by which they were instrumented to measure compression and ejection forces. The Stokes B-2 tablet machine was instrumented with integrated coupled piezoelectric transducers[3] located in the eye bolt and the ejection cam. There were three transducers placed in the cam which were wired in series to produce the output signal. Force and ejection data were processed by an Apple II plus micro-computer, interfaced to the tablet press through an Interactive Structures AI13 16 channel analog-to-digital converter. Data collection was at the rate of one data point every millisecond.

On the other hand, the Manesty B3B press used strain gauges, located on the eye bolt and the ejection cam and interfaced to an Hewlett-Packard 9000 minicomputer via a Hewlett-Packard multi-programmer. Data collection occurred at the rate of one kilo-Hertz.

The Colton Model 204 press utilized the electrostatic charge-mode type piezoelectric transducer[4], which were located in the force adjusting wheel and the ejection cam. A Gould two channel oscillograph recorder was utilized to measure the com-pression and ejection signals from the tablet press. Since, individual data points could not be obtained, numerical methods were used to calculate the area under the compression force-time curve. At least ten points were chosen from the recorded profile, and Lagrangian interpolation was done and then integrated for the area.

One kilogram of each of the blended materials was compressed at various compression forces within the range of 1.8 kiloNewtons to 21 kiloNewtons. Environmental conditions were similar for all tableting runs, 20 ± 2^{o}C and 45 ± 3 % relative humidity. Tablet punch diameter was approximately 7/16", and a tablet weight of 600 milligrams was pursuited for the Emcompress blend while a target tablet weight of 400 milligrams was used for the Avicel PH-101 cellulose mixture. These tablet weights produced tablets with similar thicknesses when compressed at the same compressional force. The maximum compression and ejection forces were obtained for at least ten tablets. In addition to monitoring these maximum forces, the areas under the force-time curves were calculated for each compression and ejection. The data was tested for reproducibility by repeating the series of compressions a minimum of four times on each tablet press.

The following tablet properties were measured from the resulting tablets: weight, thickness and hardness. A sample size of ten tablets was used to calculate the means and standard deviations of these properties.

RESULTS AND DISCUSSION

The data was anaylzed using a technique presented by Chilamkurti, Rhodes and Schwartz (3,4) to describe the shape of the compression force-time curve. This technique involves plotting the area under the compression force-time curve (Area, A) as a function of the maximum compression force (Height, H). The slope of the relationship (or A:H ratio), as determined by least squares linear regression, is thought to be probably characteristic of the material being compressed. If this is correct, then the A:H ratio could serve as a "compression finger print" for the formulation and be useful as a "trouble-shooting" tool and evaluating and classifying various pharmaceutical powders and systems.

For all the compression replicates conducted, the A:H relationships (Figures 1 and 2) were linear, having a correlation coefficient greater than 0.99. Tables 1 and 2 show the reproducibility of the A:H ratio for each of the different tablet presses utilized. The greater relative standard deviation observed for the Colton tablet press can be explained as probably due to the method used to calculate the area under the force-time curve. A covariant analysis was performed using a statistical software package from SAS[5]. The results indicated no statistical significance between the replicates, but did suggest there were significant differences (at a level of $p < .01$) between the A:H ratios for the two matrices, and the different tablet presses.

In addition to the A:H ratio, an analysis of the intercept values of this relationship was also performed. The differences observed were significant (Tables 3 and 4). While it was noted that all intercept values for the Avicel PH-101 were positive and all intercept values for the Emcompress were negative, the significance of this finding has yet to be defined. It may be concluded that the actual A:H relationship for the Emcompress may best be explained in nonlinear terms, still the linear relationship offers us a more practical approach of comparing the A:H ratios. It

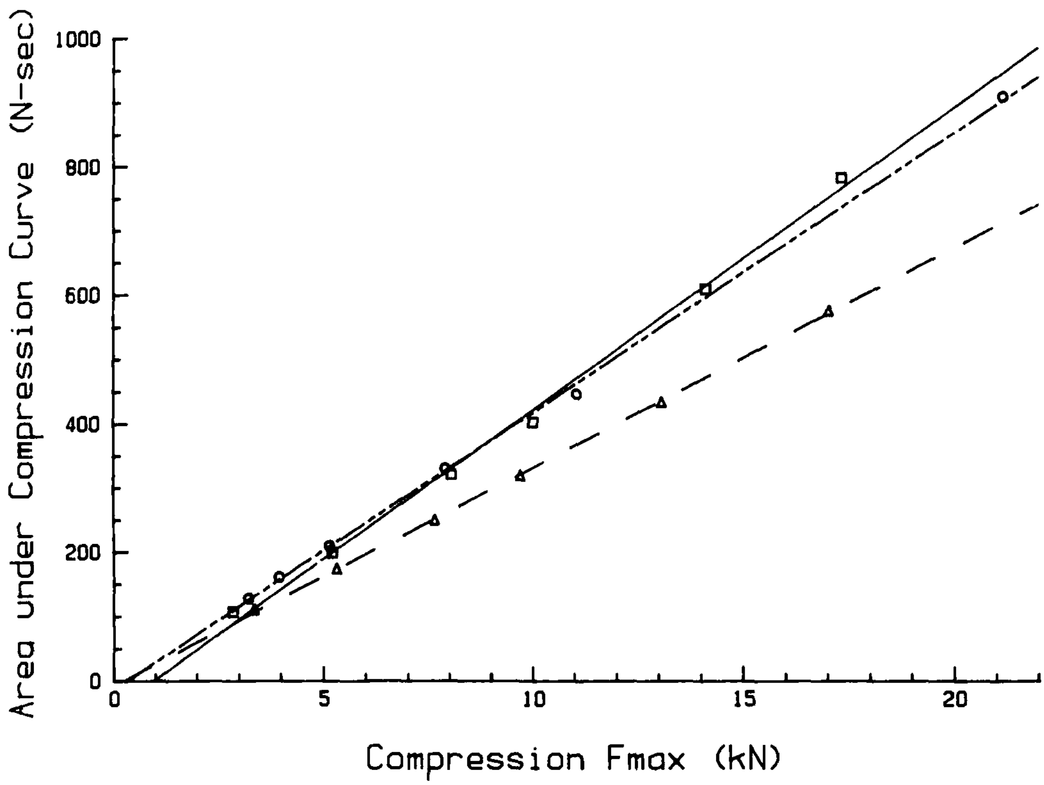

FIGURE 1

Area:Height ratios of 600mg Emcompress tablets compressed on □ Stokes B-2, △ Manesty B3B and ○ Colton 204 rotary tablet presses.

could be hypothesised that the nonlinearity of the A:H relationship may be due to a prolonged stress unloading at the higher compressional forces for Avicel PH-101 thus resulting in a proportionally higher Area, and hence a negative intercept.

Differences occurring between the Stokes B-2 and the Manesty B3B tablet presses cannot yet be explained. The two presses are similar, each has a compression roller diameter of 8.0 inches and

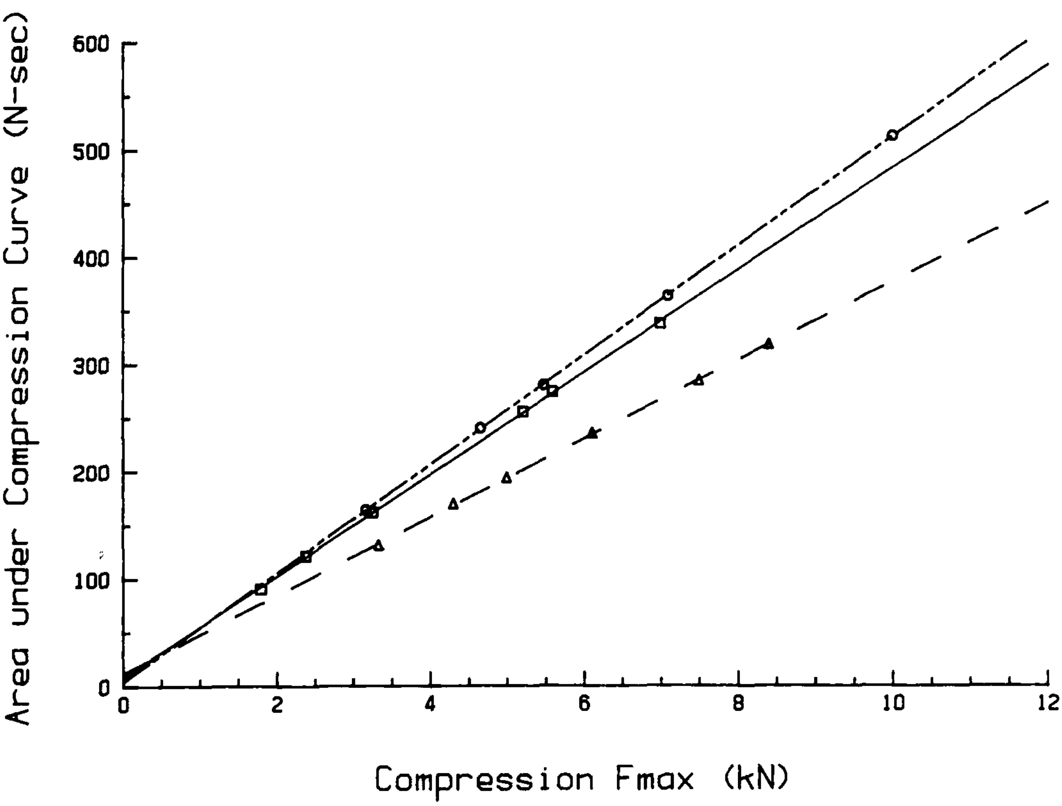

FIGURE 2

Area:Height ratios of 400mg Avicel PH-101 tablets compressed on □ Stokes B-2, △ Manesty B3B and ○ Colton 204 rotary tablet presses.

a die circle diameter of 9.0 inches. We would have expected that the geometric shape of the compression curves to be similar and hence have approximately the same area under the force-time curve at similar compression forces. The dimensions of the Colton model 204 press are, 7.5 inch compression roller diameter and a 7 11/16 inch die circle diameter. As shown in Figures 3 and 4, there are differences in the shapes of the curves. The one notable differ-

Table 1

A:H Ratio* Reproducibility for Emcompress Blend

	Replicate #							
Tablet Press	1	2	3	4	5	6	MEAN	RSD
Stokes B-2	47.08	46.72	46.60	46.14	45.98	46.26	46.46	.88
Manesty B3B	34.21	33.99	33.86	34.13	-	-	34.05	.45
Colton	43.28	43.26	41.16	44.34	-	-	43.01	3.10

* Note: units are 10^{-3} seconds

Table 2

A:H Ratio* Reproducibility for Avicel PH-101 Blend

Tablet Press	Replicate # 1	2	3	4	5	6	MEAN	RSD
Stokes B-2	47.90	47.94	47.54	48.16	48.00	47.70	47.88	.46
Manesty B3B	36.56	36.09	36.53	36.64			36.45	.68
Colton	49.55	50.17	51.48	50.71			50.48	1.62

* Note: units are 10^{-3} seconds

Table 3

Intercept Values* for A:H Ratio for Emcompress Blend

Tablet Press	Replicate # 1	2	3	4	5	6	MEAN	RSD
Stokes B-2	-29.76	-44.26	-43.40	-42.58	-40.76	-43.36	-44.18	6.75
Manesty B3B	-8.26	-7.46	-6.16	-8.59			-7.62	14.20
Colton	-14.15	-13.45	-8.62	-22.76			-14.75	39.89

* Note: units are Newton-seconds

Table 4

Intercept Values* for A:H Ratio for Avicel PH-101 Blend

Tablet Press	Replicate # 1	2	3	4	5	6	MEAN	RSD
Stokes B-2	8.52	7.18	7.86	6.52	7.08	8.70	7.64	11.29
Manesty B3B	10.84	13.52	11.77	9.84			11.49	13.61
Colton	7.62	7.17	1.21	4.88			5.22	56.13

* Note: units are Newton-seconds

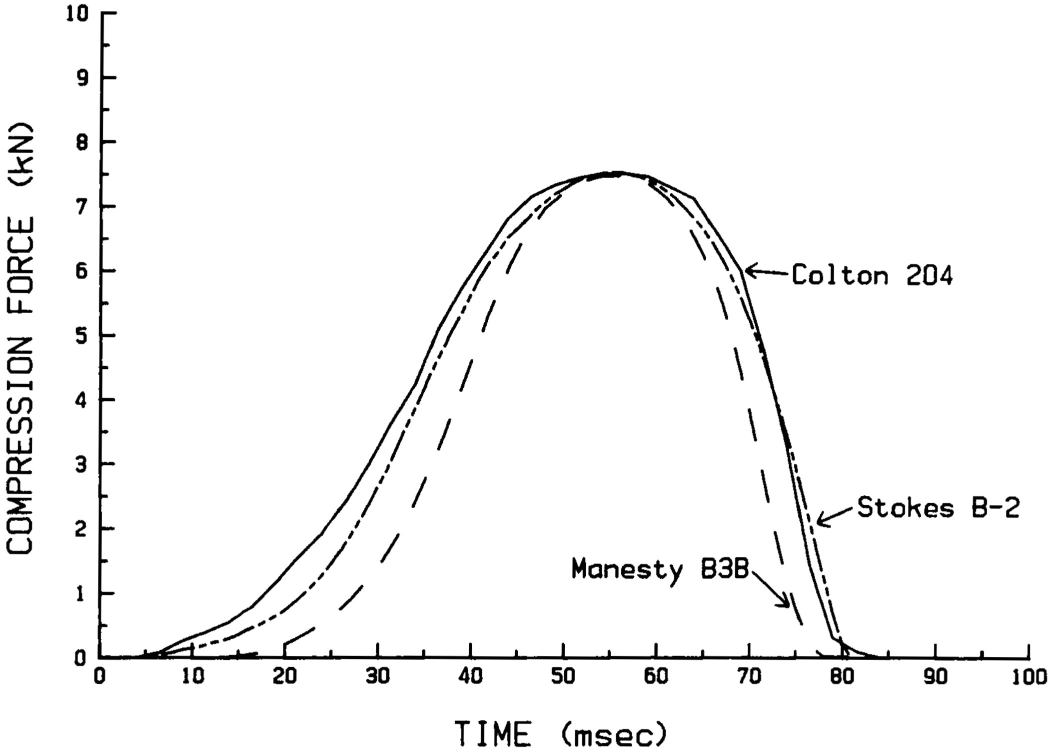

FIGURE 3

Compression curves of 600mg Emcompress tablets compressed at a maximum force of 7.5 kN on (a) Stokes B-2, (b) Manesty B3B and (c) Colton 204 rotary tablet presses. The peaks of each curve have been adjusted to occur at the same time point.

ence between the Stokes B-2 and the Manesty B3B presses utilized in the study was that the length of the lower punch shanks, the Stokes B-2 utilized the shorter ("stubbie") lower punches while the Manesty B3B used the longer punch. It is doubtful that this would have caused such a significant difference between the two presses.

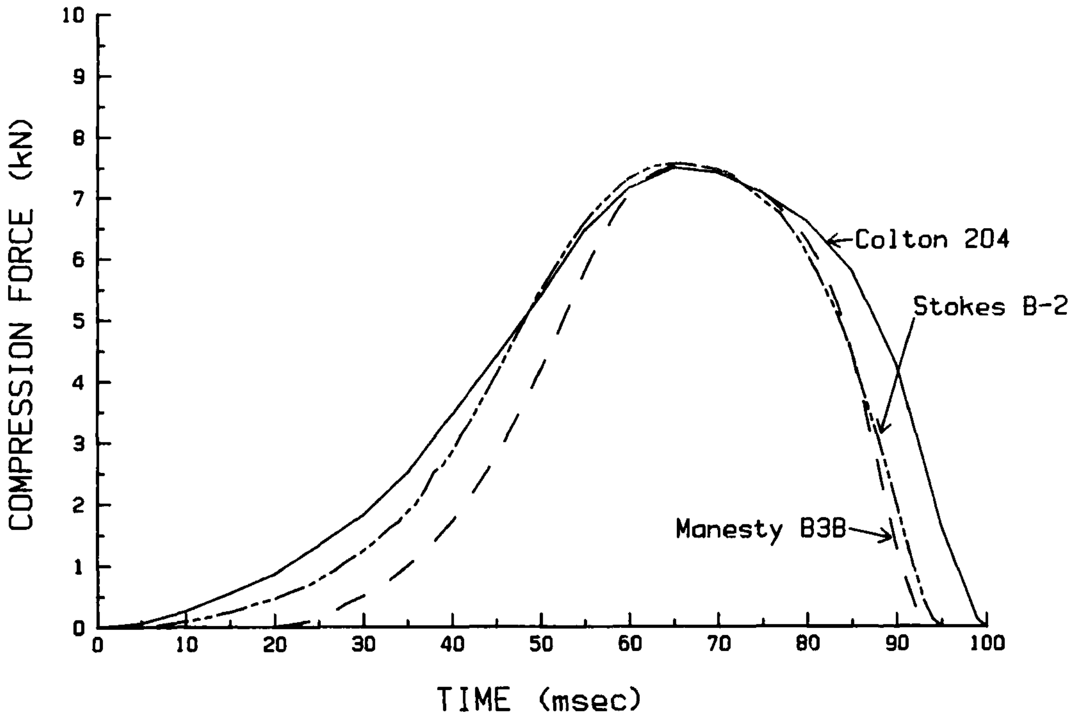

FIGURE 4

Compression curves of 400mg Avicel PH-101 tablets compressed at a maximum force of 7.5 kN on (a) Stokes B-2, (b) Manesty B3B and (c) Colton 204 rotary tablet presses. The peaks of each curve have been adjusted to occur at the same time point.

Figure 5 shows the difference in the shapes of the compression profiles for the two matrices while compressed on the Stokes B-2 tablet press at a compression force of 7.5 kN. Similar differences were observed for the Manesty B3B and Colton 204 tablet presses. At this particular force, the ratio of the areas for Avicel PH-101: Emcompress are similar for the Stokes B-2 and

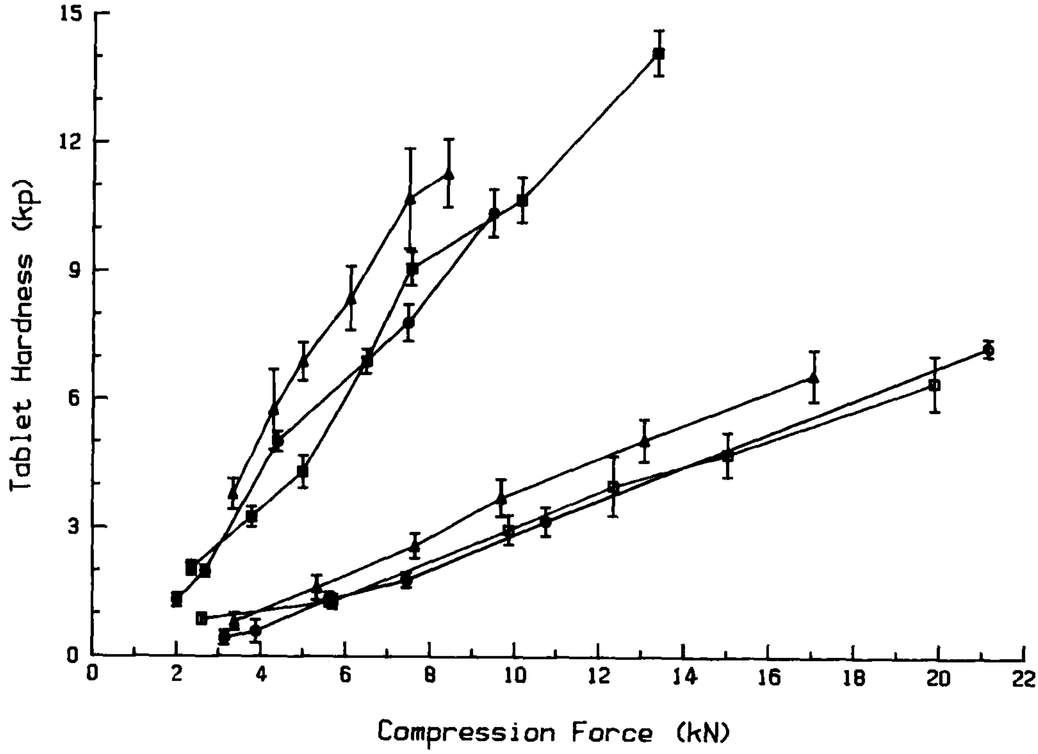

FIGURE 5

Tablet hardness profiles of tablets. Emcompress tablets compressed on □ Stokes B-2, △ Manesty B3B and ○ Colton 204 presses. Avicel PH-101 tablets compressed on ■ Stokes B-2, ▲ Manesty B3B and ● Colton 204 rotary tablet presses.

Manesty B3B tablet presses. This observation was not made at any other compression force and may perhaps just a coincidence.

Figure 6 shows the slight differences that were seen in the resultant hardnesses of the tablets. These differences, upon analysis were not statistically significant. There does not appear to be any rational order to the relationship between the rank order of the A:H ratio and the hardness.

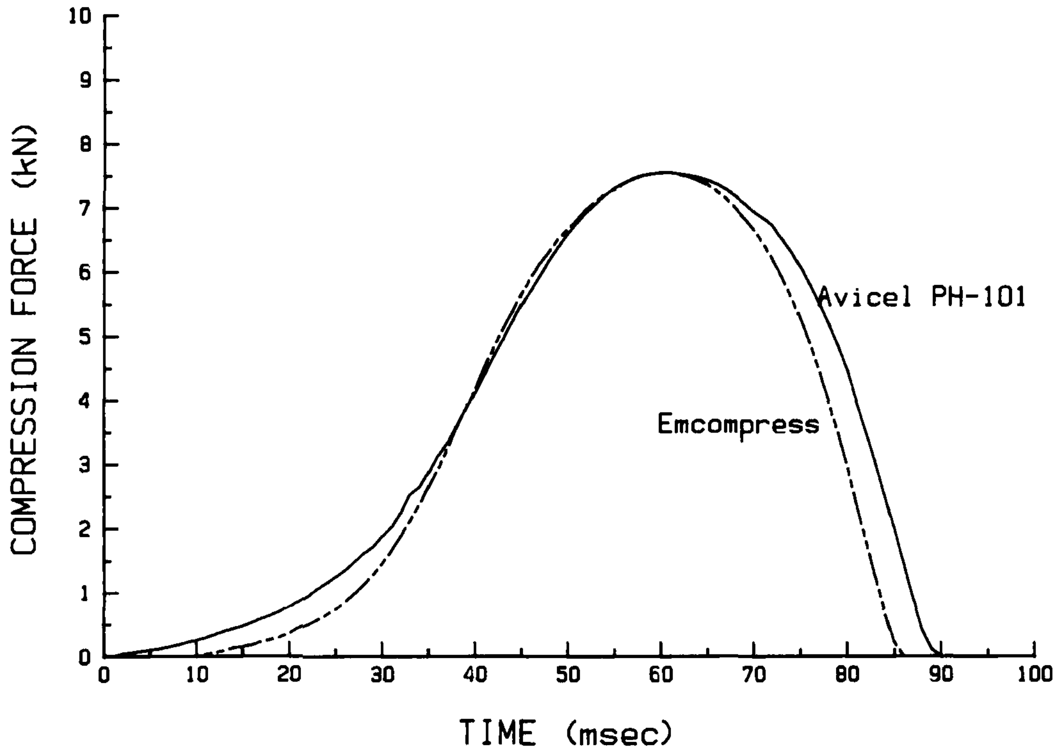

FIGURE 6

Compression curves for (a) Emcompress and (b) Avicel PH-101 tablets compressed on a Stokes B-2 rotary tablet press. The peaks of the curves have been adjusted to occur at the same time point.

An example of the ejection force curves for each of the tableting runs is shown in Figure 7. The shapes of the ejection force curves obtained clearly show differences in the level of lubricity of the two systems. At compression forces greater than 10.0 kN, capping was observed for tablets made from the Avicel PH-101 blend. This is probably the due to overlubrication of the system, resulting in the lubricant interfering with the bonding capacity of the Avicel PH-101.

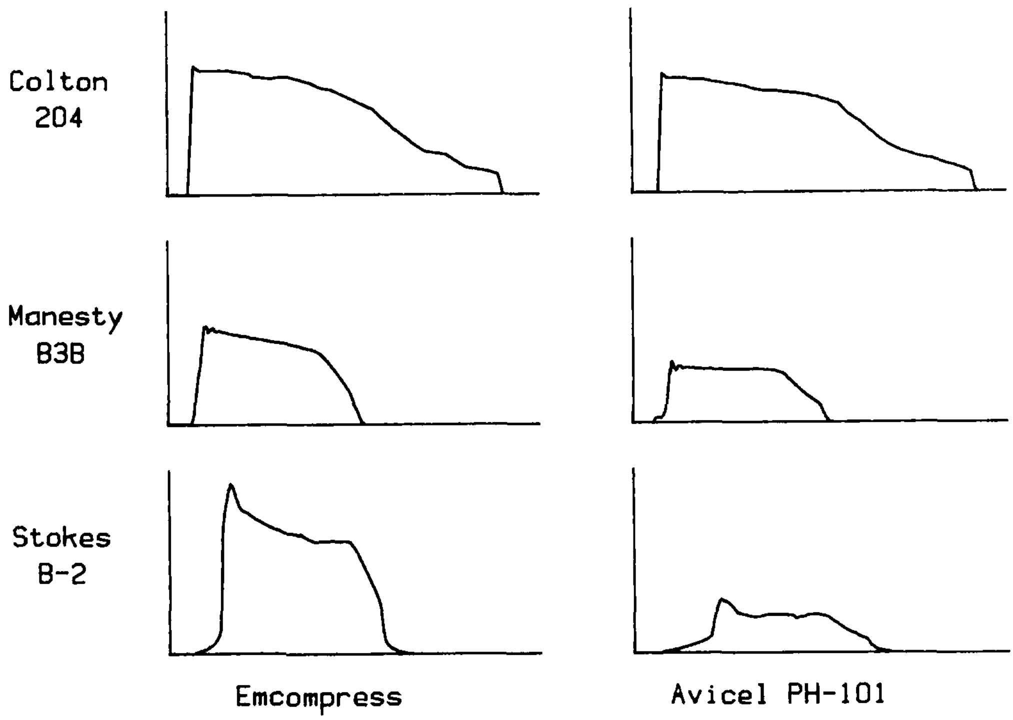

FIGURE 7

Ejection curves of Emcompress and Avicel PH-101 compressed at a force of 7.5 kN on three tablet presses.

One of the possible causes for the differences existing in the A:H ratios between the Stokes B-2 and the Manesty B3B presses was thought to be the depth of upper punch penetration. An experiment to test this hypothesis was conducted. An Emcompress blend was compressed at the following punch penetration depths: 1/8", 3/16", 1/4", 5/16", and 3/8 inches. The resultant weight tablet was maintained at 600 milligrams and the press was operated at 30 rpms. Analysis of the results using a heterogenity of slope model in the General Linear Models procedure of SAS[5] was con-

Table 5

Results of General Linear Model Analysis[5]

Source	df	Sum of Squares	F value	PR > F
Due to Regression	1	13846647.35	99999.99	1E-70
Between A:H Intercepts	4	109.24	0.21	0.9316
Between A:H Slopes	4	1208.48	2.35	0.0553
Error	240	30914.71		
Total	249	13878879.78		

A:H Parameter	Punch Penetration[1]	Estimate[2]	Standard Error
Slope	1/8	58.07	0.39
	3/16	58.25	0.39
	1/4	56.92	0.40
	5/16	57.73	0.40
	3/8	58.47	0.39
Intercept	1/8	-47.83	3.62
	3/16	-43.17	3.60
	1/4	-45.28	3.69
	5/16	-45.81	3.70
	3/8	-45.64	3.61

Notes: Units
1- inches
2- for A:H Slope: x 10^{-3} seconds
for Intercept: Newton-seconds

ducted. Table 5 shows the results, which indicate that the upper punch penetration did not significantly alter the area of the compression force-time curve and the A:H ratio. This could be explained as it is the distance between the upper and lower punches that determines the compression force for a given amount of material. As the punch penetration is increased, then the height of the lower compression roller is lowered to maintain the desired compression force. The important finding of this experiment was that the shape of the compression force-time curve was not affected by the depth of punch penetration.

The main thrust of this paper has been to investigate in a preliminary way the parity of data from different tablet presses. In a later paper, presently in prepartation, we will explore in some detail the advantages and limitations of modes of interpreting data from instrumented tablet presses. In particular, attention will be directed to the utility of Area:Height values.

CONCLUSIONS

The results from this study clearly show the value of the derived compaction parameter, Area:Height ratio. This and several other derived parameters are likely to aid in the understanding of the shape of compression profiles in future studies. However more work is obviously needed to explore the relationship between powder properties and compaction data.

It is premature to attempt to derive definitive conclusions from the observations made in this study. However, it is already apparent from this study that although there are differences between data derived from the three presses, these differences are relatively small and thus there is good reason to believe that with or without some type of correction factor, the data from different presses can be reliably compared, at least in a semi-quantitative manner.

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FOOTNOTES

1. Avicel PH-101, FMC Corporation, Philadelphia, PA.
2. Emcompress, Edward Mendell Co., Carmel, NY.
3. Piezotronics, Inc., Depew, NY.
4. Kistler Instrument Corporation, Amherst, NY.
5. SAS (Statistical Analysis Systems) Institute, Cary, NC.

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