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RESEARCH PAPER

New Parameters Derived from Tablet Compression Curves. Part I. Force–Time Curve

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ABSTRACT

A great number of new parameters derived from tablet force–time curves are introduced. The crushing strength and friability of tablets were measured, and the dependence between the calculated compression parameters and the two tablet properties was studied. Tablets were made with an instrumented eccentric tablet machine using three different compression forces and three different compression speeds. The testing material was α-lactose monohydrate. This seems to be a limitation in this study, but our main purpose was to introduce these new compression parameters. The results showed that the suggested parameters described clearly different patterns of material behavior. We suggest that, especially together, these parameters may be used in the prediction of compression characteristics of different materials.

INTRODUCTION

Parametrization of tablet force–time profiles has been under continuous research (1–4). Recently, most of these studies have used rotary tablet machines in which the instrumentation is still quite difficult. However, studies have been performed also with eccentric tablet machines (5–8), although these parametrizations have been quite limited. According to Hoblitzell and Rhodes (3), compression profiles may act as formulation "fingerprints" and aid in troubleshooting. This suggests a general value for the parametrization of tablet compression force–time profiles.

Despite extensive research, the basic questions still seem to be open. Is it possible to obtain some basic parameters from the force–time curve in order to predict compression characteristics of different types of materials? How well can the most important mechanical properties of tablets be estimated from force–time curves? And, is it possible to predict the compression behavior of materials in high-speed rotary machines on the basis of compression data obtained from eccentric tablet machines?

A primary purpose in parametrization of the force–time profiles has been to obtain general material parameters which can be used in the evaluation of tableting behavior of powders or granules. In product development, preliminary research is often made using eccentric single-punch tablet machines, but in production scale, only high-speed rotary presses are used. Therefore, it would be important to be able to parameterize and first to understand the relevance of the compression profiles of eccentric tablet machines. Thereafter, it may be possible to broaden the studies and use these parameters when studying the compression behavior of materials in rotary tablet machines. This kind of modeling may be complex by traditional methods, because the whole problem consists of simultaneously affecting factors which are hardly additive and presumably even nonlinear. Fortunately, the use of neural networks seems to give promising new possibilities for solving complicated multivariate problems (9,10).

The purpose of this preliminary study was to introduce a number of new different parameters calculated from tablet force–time curves and to explain the crushing strength and friability of lactose tablets by these parameters.

MATERIALS AND METHODS

The test material used was 80-mesh α-lactose monohydrate (EMW, Veghel, the Netherlands). One percent of magnesium stearate was added as a lubricating agent.

The filler material and magnesium stearate were mixed in a Turbula mixer (System Schatz, Willy A. Bachhofen, Switzerland). The filling capacity of the mixer was 70% and mixing time 2 min. After mixing, the mass was stored in controlled conditions for 3 days in a relative humidity of 45 ± 1% and a temperature of 20 ± 0.5°C (Ehret, KBK 4330, Dipl. Ing. W. Ehert GmbH, Emmendingen, Germany). Before tablet compression, the moisture content of the mass was determined (Sartorius Universal, Type U3600, Sartorius GmbH, Göttingen, Germany).

Tablets were compressed with an instrumented eccentric tablet machine (Korsch EK0, Erweka Apparatebau, Germany) using flat-faced punches with a diameter of 9 mm. Compression forces were 11, 15, and 19 kN, and compression speeds 10, 20, and 40 rpm. In each case, force–time curves and upper punch displacement were determined from 5 tablets. The target height of the tablets was 4.0 mm.

The measured responses of the tablets were crushing strength (n = 10, Schleuniger-E, Switzerland) and friability (n = 20, Friabilator, Ernst-Keller & Co. AG, Basel, Switzerland, using 100 revolutions).

Modeling

Because the raw force–time curves had some disturbances, the upper and lower punch force curves were first filtered using a floating 5-point smoothing. A summary of the calculated compression parameters is given in Tables 1 and 2, and in Figs. 1 and 2. All parameters were calculated using Mathcad v. 5.0 Plus (MathSoft Inc., USA), and the drawings and curve fittings were made with SigmaPlot v. 2.01 (Jandel Scientific GmbH, Germany). Correlation analyses were calculated with SYSTAT v. 5.0 (SYSTAT Inc., USA), and regression models were made with MODDE v. 3.0 (Umetri AB, Sweden).

The initial regression model (Y) for the two independent variables used in the study was as follows:

$$Y(F,t) = a_0 + a_1F + a_2t + a_3Ft + a_4F^2 + a_5t^2 \quad (1)$$

where $a_0, \ldots, a_5$ are coefficients, and F and t denote the effective compression force and compression time, respectively.

The models were simplified by a normal stepwise technique. Each term included in the final regression model was tested with the t test. The primary idea was to include only significant terms ($p < 0.05$). However, if a certain second-order term was chosen for the model, then the linear term of that factor was also included. Before statistical analysis the independent variables were normalized to −1 and +1.

Description of Calculated Parameters

The summary of calculated force–time compression parameters is given in Table 1.

Effective force F_{eff} was calculated as a geometrical mean [Eq. (2)] of upper punch force F_{up} and lower punch force F_{lp}:

Table 1

Parameters Calculated from the Force–Time Compression Curves

Parameter	Symbol	Unit
Upper punch force	F_{up}	N
Lower punch force	F_{lp}	N
Effective force	F_{eff}	N
Reflected force	$F_{eff,e}$	N
Maximum of the effective force	$F_{eff,max}$	N
Time for the maximum upper punch displacement	t_{max}	msec
Time when the $F_{eff,max}$ is achieved	$t_{Feff,max}$	msec
The width at half-height of F_{eff} (the left side)	t_{LFeff}	msec
The width at the half-height F_{eff} (the right side)	t_{RFeff}	msec
Elasticity factor calculated from t_{LFeff} and t_{RFeff}	E_{Feff}	—
Area of the F_{eff} curve before time t_{max}	A_1	N msec
Area of the F_{eff} curve after time t_{max}	A_2	N msec
Area difference of ideal elastic and real material after time t_{max}	A_3	N msec
Relative elasticity calculated using area values A3 and A1	RE_{Feff}	%

$$F_{eff} = \sqrt{F_{up}F_{lp}} \tag{2}$$

It is assumed that the use of effective force will minimize the effects of the unhomogeneous structure of compressed tablets. This unhomogeneous structure results, for example, from the die wall friction, particle orientation during compression, and partial melting and recrystallization of materials at contact points. Also, particles will have more freedom to change their position and orientation on the main axis of the die cylinder.

Area A_1 (Fig. 1) is an integral of the effective force–time curve during the consolidation phase and can thus be calculated with the following formula:

$$A_1 = \int_0^{t_{max}} F_{eff}\, dt \tag{3}$$

Table 2

Parameters Calculated from the Difference Force–Time Curves

Parameter	Symbol	Unit
Force difference curve	F_{diff}	N
Maximum of the force difference curve	$F_{diff,max}$	N
Normalized $F_{diff,max}$	NF_{diff}	—
Time when F_{diff} is no longer detected (F_{diff} < 5 N)	$tmax_{Fdiff}$	msec
Time when the $F_{diff,max}$ is achieved	$t_{Fdiff,max}$	msec
Normalized $t_{Fdiff,max}$	$Nt_{Fdiff,max}$	—
The width at half-maximum of F_{diff} (the left side)	t_{LFdiff}	msec
The width at half-maximum of F_{diff} (the right side)	t_{REdiff}	msec
Normalized time difference for t_{LFdiff} and t_{REdiff}	Δt_{NFdiff}	—
Elasticity factor calculated from t_{LFdiff} and t_{RFdiff}	E_{Fdiff}	—
Area of the F_{diff} curve before time $t_{Fdiff,max}$	a_1	N msec
Area of the F_{diff} curve after time $t_{Fdiff,max}$	a_2	N msec
Proportion of area a_1 on the total area $a_1 + a_2$	G_1	—
Ratio of parameters a_1 and a_2	G_2	—

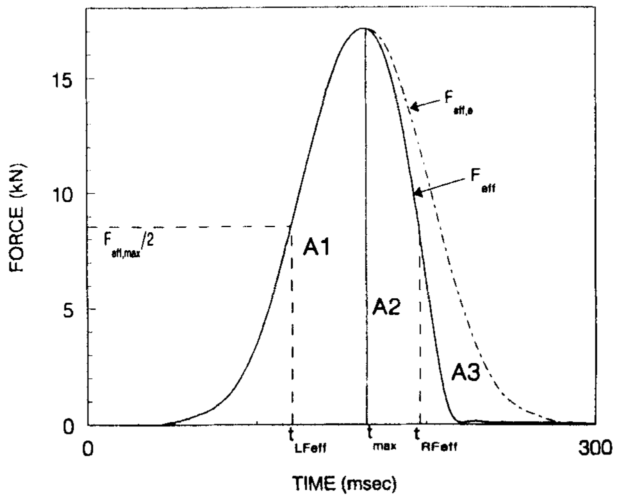

Figure 1. Definition of the parameters calculated from the force–time curve.

where t_{max} represents the time point when the upper punch has achieved maximum displacement. This is not the same as the time point where the maximum force is achieved ($t_{Feff,max}$), because irreversible changes occur also during the consolidation phase. The time point

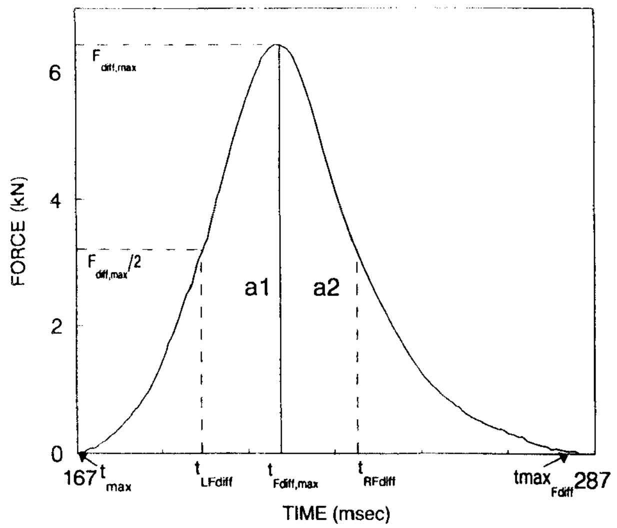

Figure 2. Definition of the parameters calculated from the difference force–time curve.

$t_{Feff,max}$ is always achieved slightly earlier than t_{max}. Kala et al. (8) earlier used almost the same kind of parameterization for force-time curves, but they assumed that the maximum compression force and maximum punch displacement occur at the same time point. The area value A_2 [Eq. (4)] is the area under the curve of the effective force–time curve after time point t_{max}. Integration can be made to infinity but, because the compression curve always achieves the value 0 during time $2t_{max}$, we used this as a higher integration limit. This was done because thus we received more accurate values for the integrals.

$$A_2 = \int_{t_{max}}^{2t_{max}} F_{eff}\, dt \tag{4}$$

Area A_3 can be calculated using the following equation:

$$A_3 = \int_{t_{max}}^{2t_{max}} (F_{eff,e} - F_{eff})dt \tag{5}$$

where $F_{Feff,e}$ represents a compression curve of an ideal elasticity system after time t_{max} (Fig. 1). This ideal system has a totally symmetrical compression curve. We do know that this cannot be exactly the case in practice, because some irreversible changes occur during the early stage of compression. Naturally, A_3 is always smaller than A_1, and the above-mentioned three parameters are linked together simply as $A_3 = A_1 - A_2$.

Next we define relative elasticity, RE_{Feff}, which can have values from 0% to 100%. For an ideal elastic material this value is 100%, and for a system which undergoes total irreversible deformation without any elastic nature this parameter has a value 0%. Naturally all real systems are between these extreme limits.

$$RE_{Feff} = 100 \cdot \left(1 - \frac{A_3}{A_1}\right)\% \tag{6}$$

Elasticity factor E_{Feff} was calculated using two time differences presented more clearly in Fig. 1:

$$E_{Feff} = \frac{t_{RFeff} - t_{Feff,max}}{t_{Feff,max} - t_{LFeff}} \tag{7}$$

For ideal rubber elastic material this parameter gives the value 1, and for totally fragmented material the value 0.

In theory, if different compression speeds are used, this parameter may also give rough information on the relative amount of plastic deformation and fragmentation of materials.

Equations Calculated from Difference Force–Time Curves

The summary of parameters calculated from difference force–time curves is given in Table 2.

The difference force–time curve between the absolute elastic system and the real tablet compression curve after the maximum punch displacement is:

$$F_{diff} = F_{eff,e} - F_{eff} \quad (8)$$

where $F_{eff,e}$ corresponds to the totally elastic system and is a reflected force–time curve of the consolidation phase (Fig. 2).

Factor NF_{diff} is a normalized dimensionless parameter [Eq. (9)], which has a value 1 for nonelastic systems and 0 for elastic systems. Also this parameter may thus give information on the quantification of elastic/nonelastic behavior of materials:

$$NF_{diff} = \frac{F_{diff,max}}{F_{eff,max}} \quad (9)$$

We suggest that the dimensionless normalized parameter $Nt_{Fdiff,max}$ [Eq. (10)] may give information on the relative magnitude of plasticity and fragmentation of material, because plastic deformation is a time-dependent phenomenon and fragmentation is considered to occur immediately:

$$Nt_{Fdiff,max} = \frac{t_{Fdiff,max} - t_{max}}{t\ max_{Fdiff} - t_{max}} \quad (10)$$

The full-width at the half-maximum of the difference curve [Eq. (11)] may also give information on material behavior. Especially the usefulness of this parameter could be tested using different materials and certain fixed compression speeds. Thus this parameter may have a rather limited value in this study.

$$\Delta t_{Fdiff} = t_{RFdiff} - t_{LFdiff} \quad (11)$$

A more useful parameter is obviously Δt_{NFdiff}, because it is normalized with the width of the difference curve (in time units). For ideal elastic materials this parameter has a value 0. The higher values show irreversible deformation during compression.

$$\Delta t_{NFdiff} = \frac{\Delta t_{Fdiff}}{t\ max_{Fdiff} - t_{max}} \quad (12)$$

The next parameter, elasticity factor E_{Fdiff}, is calculated using time differences related to the half-maximum force of the difference compression curve (Fig. 2) as follows:

$$E_{Fdiff} = \frac{t_{RFdiff} - t_{Fdiff,max}}{\Delta t_{Fdiff}} \quad (13)$$

The next two equations give numerical values for the areas calculated from the difference curve [parameters a_1 and a_2 in Fig. 2 and Eq. (14 and (15)]. Parameter a_1 will give higher values for plastic materials in which the changes are time dependent.

$$a_1 = \int_0^{t_{Fdiff,max}} F_{diff}\, dt \quad (14)$$

$$a_2 = \int_{t_{Fdiff,max}}^{t_{Feff,max}} F_{diff}\, dt \quad (15)$$

These values and their sum may be valuable and can possibly be related to the work done during compression. However, in this paper we use only parameters G_1 and G_2 [Eqs. (16) and (17)] which are simple ratios of the areas a_1 and a_2. These parameters can presumably also give information on the time-dependent changes in the powder bed and bond formation during tablet compression.

$$G_1 = \frac{a1}{a1 + a2} \quad (16)$$

$$G_2 = \frac{a1}{a2} \quad (17)$$

The difference between the two parameters may be minimal, and the simpler parameter G_2 may be more sensitive, because G_1 has area a_1 both in the denominator and in the divisor, and it may thus partly hinder the effect of area a_2.

RESULTS AND DISCUSSION

Correlation coefficients according to Pearson and the corresponding p values of the calculated parameters for crushing strength and friability are given in Table 3. The highest correlations ($R > 0.92$, $p < 0.0000$) for crushing strength and friability were obtained for G_2, G_1, E_{Fdiff}, and $Nt_{Fdiff,max}$. It should be noticed that responses f as a function of different arguments x were described using as simple models as possible. The models used were linear: $f(x) = ax + b$, quadratic: $f(x) = a\,x^2 + bx + c$, or exponential; $f(x) = a\,e^{(-b\,x)} + c$ or $f(x) = a(1 - e^{(-b\,x)}) + c$, where a, b, and c are different constants. The model was selected so as to describe the experimental data most accurately.

In all cases the crushing strength and friability of tablets behaved logically: with increasing crushing strength the friability decreased. Partly for that reason we present the effect of the selected parameters on these two responses parallelly.

Parameters Derived from Force–Time Curves

Influences of the elasticity factor (E_{Feff}) and relative elasticity (RE_{Feff} in %) are given in Figs. 3 and 4. Both parameters have a nonlinear effect on the responses. We believe that these parameters will have a great importance in the future because they can be used to quantify the irreversible changes during tablet compression. The responses used here had quite large standard deviations. Many other tablet characteristics may behave in a much more stable way.

A surface plot (Fig. 5) shows the dependence of relative elasticity as a function of $F_{eff,max}$ and compression time ($R^2 = 0.67$). When slow compression speeds are used, the relative elasticity is not dependent on the maximum effective force. But with higher compression speeds the relative elasticity is highly dependent effective compression force. This is understandable, because with high compression forces and short compression times, a smaller relative amount of work done to the system is bound irreversibly in the tablet.

Parameters Derived from Difference Force–Time Curves

The elasticity factor E_{Fdiff} (Fig. 6) seems to have a linear correlation with crushing strength but a quadratic

Table 3

Pearson Correlation Coefficients (R) of the Calculated Compression Parameters, Corresponding p Values and Model Type (M) for Crushing Strength and Friability of Tablets

Parameter	Crushing Strength			Friability		
	R	p	M[a]	R	p	M[a]
E_{Feff}	0.893	0.0001	Q	-0.895	0.0001	Q
RE_{Feff}	-0.838	0.0003	Q	0.811	0.0008	Q
$F_{diff,max}$	0.767	0.0022	Q	-0.808	0.0008	Q
NF_{diff}	-0.798	0.0009	Q	0.780	0.0019	Q
$Nt_{Fdiff,max}$	0.927	0.0000	E	-0.925	0.0000	E
E_{Fdiff}	-0.984	0.0000	L	0.973	0.0000	Q
Δt_{NFdiff}	-0.652	0.0329	L	0.619	0.042	L
G_1	0.989	0.0000	Q	-0.975	0.0000	Q
G_2	0.990	0.0000	Q	-0.977	0.0000	Q

[a]Linear model (L) : $f(x) = ax + b$. Quadratic model (Q) : $f(x) = ax^2 + bx + c$. Exponential model (E): $f(x) = ae^{-bx} + c$ or $f(x) = a(1 - e^{-bx}) + c$. a, b, c are different constants.

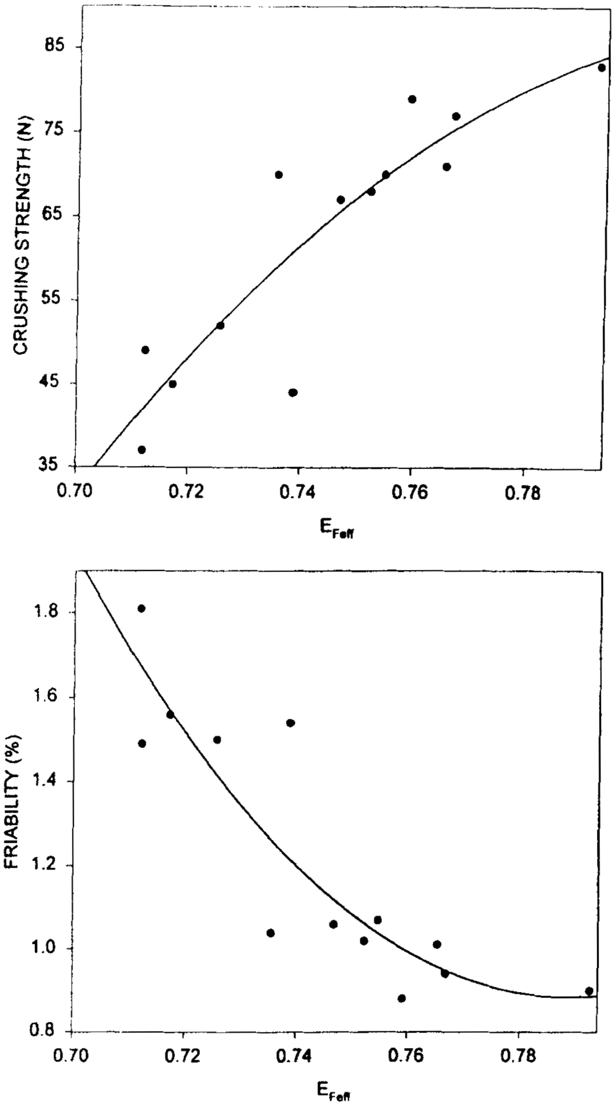

Figure 3. Elasticity factor (E_{Feff}) calculated from parameters t_{LFeff} and t_{RFeff}.

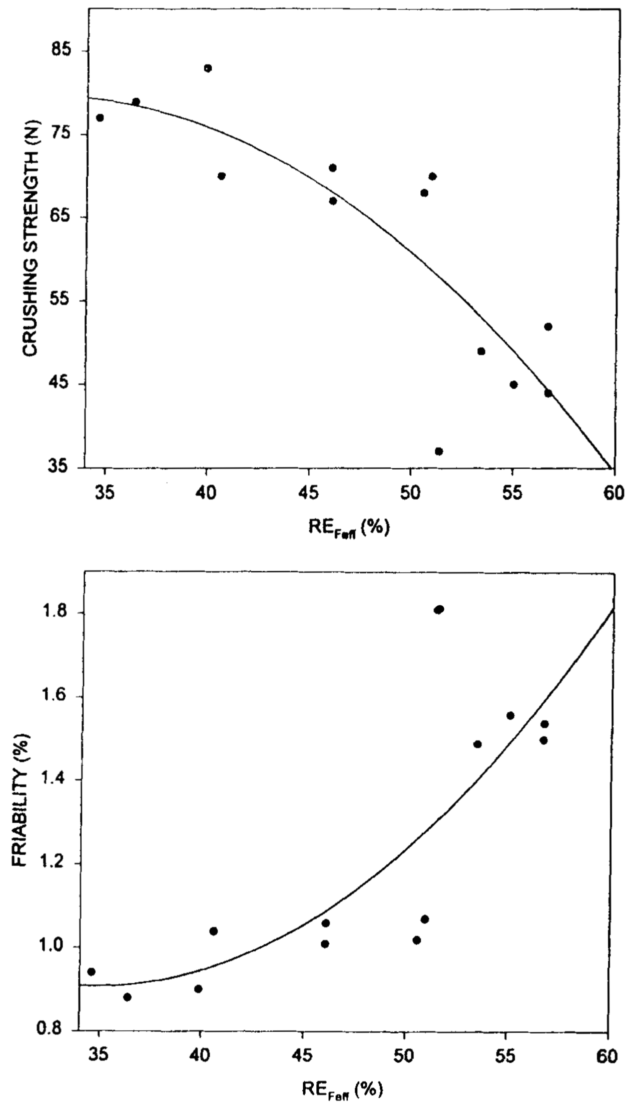

Figure 4. Relative elasticity (RE_{Feff} in %) calculated using area values A3 and A1.

dependence on friability. This is an exception, because usually both responses have the same type of dependence on the compression parameters. So far, we have not found any acceptable explanation for this. The most evident explanation is a too limited experimental region. If it had been possible to use a wider region, both responses would quite certainly have had exponential dependences. A very slight quadratic dependence between crushing strength and E_{Fdiff} can be found but, in fact, the explanation degree will be the same as for the linear model. According to Fig. 7, the elasticity factor E_{Fdiff} (R^2 = 0.84) is dependent on the compression time, es-

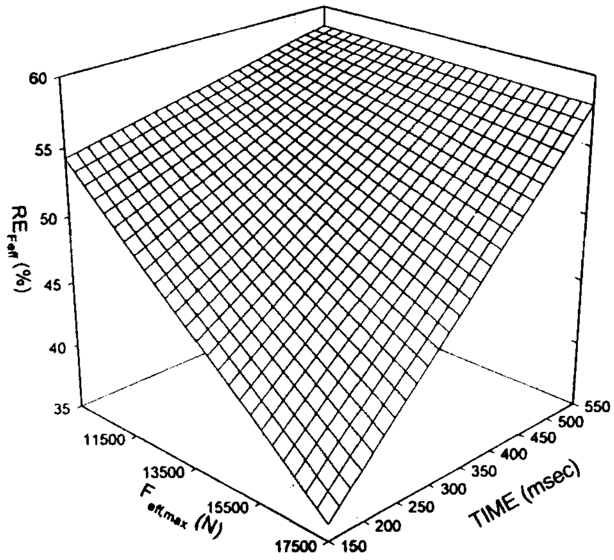

Figure 5. Relative elasticity as a function of $F_{\text{eff,max}}$ and compression time ($R^2 = 0.67$).

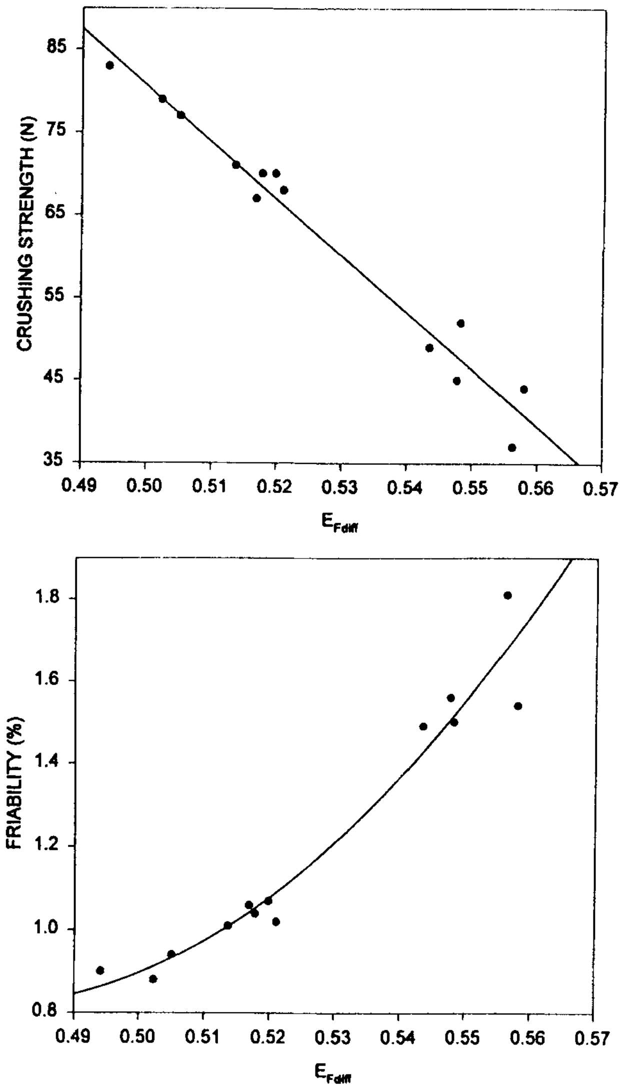

Figure 6. Elasticity factor (E_{Fdiff}) calculated from t_{LFdiff} and t_{RFdiff}.

pecially when high compression forces are used. The influence of maximum effective force is evident and quite expected. This parameter seems to give mainly the same information as did earlier the relative elasticity (Fig. 5). How these parameters will correlate with other materials is unknown.

Parameter G_2, which is a simple ratio of surface area a_1 and a_2 (Fig. 8), had the highest R^2 values. The models used for both responses are quadratic (Table 3). This parameter (like parameter G_1) can obviously give information on the time-dependent changes in the powder bed and bond formation during tablet compression. For totally fragmented material this parameter will have the value 0, and for real tablets higher values. For rubber-elastic material this parameter cannot be defined. These parameters (with some others) may be used in quantitation of the relative amount of fragmentation and plastic deformation of materials during tablet compression.

Normalized $Nt_{\text{Fdiff,max}}$ parameters were modeled using exponential functions (Fig. 9). A major effect seen in the figure is that if stronger tablets are to be made, the value of $Nt_{\text{Fdiff,max}}$ must be higher.

Figures 10 and 11 show normalized force–time and normalized difference force–time profiles for tablets which have different crushing strengths. These figures

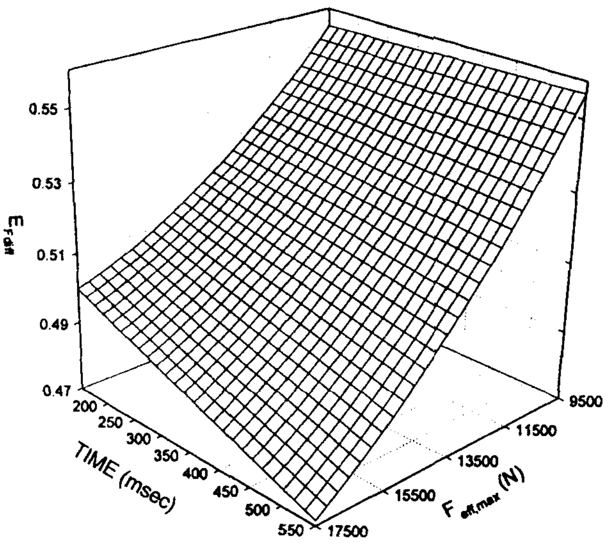

Figure 7. Elasticity factor (E_{Fdiff}) as a function of compression time and maximum effective force (R^2 = 0.84).

show how the general shape of the curve profiles changes as the crushing strength varies from 37 to 83 N. This may also give new possibilities for the evaluation of the behavior of materials under compression.

The greatest limitation in this study is that we have been able to use only one test material, α-lactose monohydrate. The general applicability of the compression parameters would require comprehensive studies in the future with different types of materials.

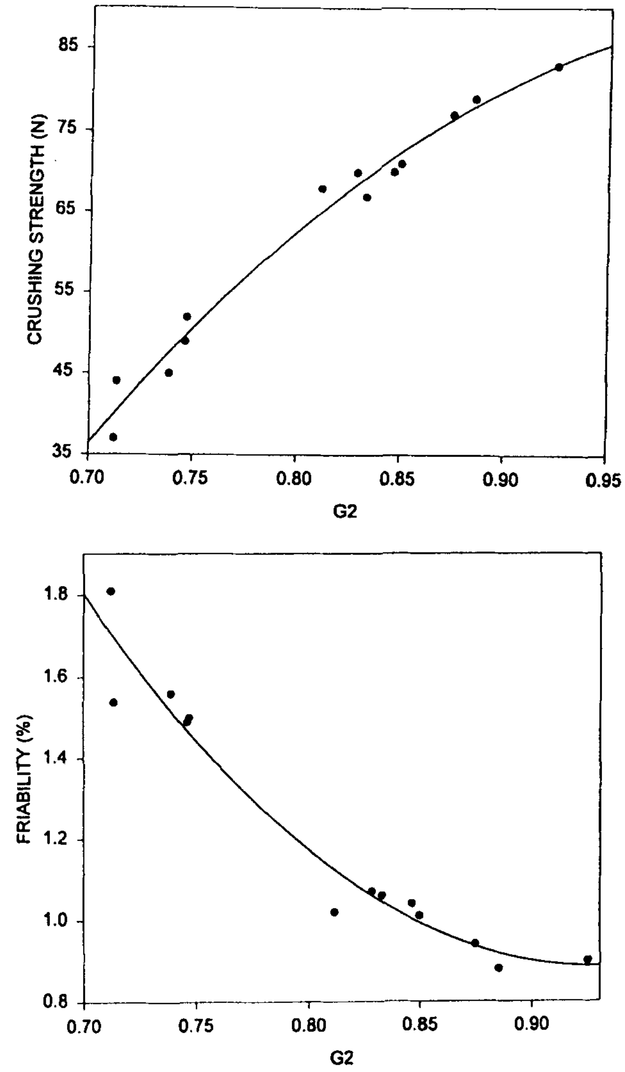

Figure 8. Parameter G_2 calculated using surface areas (a_1 and a_2) of the difference force–time curve.

CONCLUSIONS

On the basis of this study, we do believe that many of our new compression parameters can, in certain cases separately, but more presumably together, give totally new possibilities for characterizing behavior of powders during compression. One basic aim in such future studies should be to find the most essential compression parameters using simple eccentric machines and to model and correlate the results for high-speed rotary machines. In such cases, advanced data analysis and modeling will be necessary. For example, the use of neural networks, with the most basic back-propagation

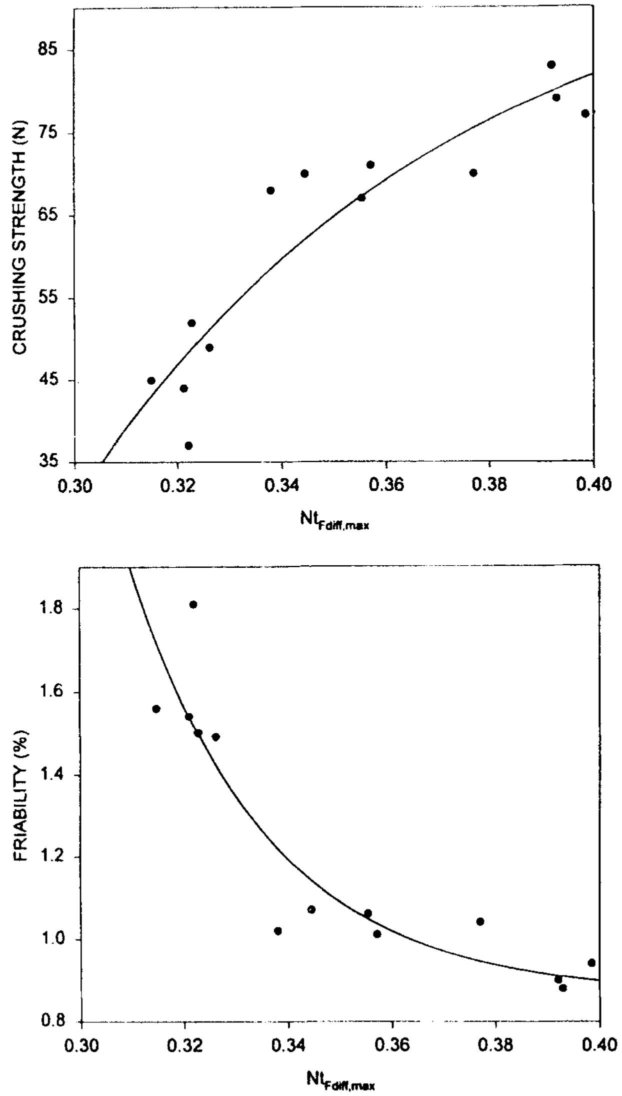

Figure 9. Normalized $t_{Fdiff,max}$ parameter, $Nt_{Fdiff,max}$.

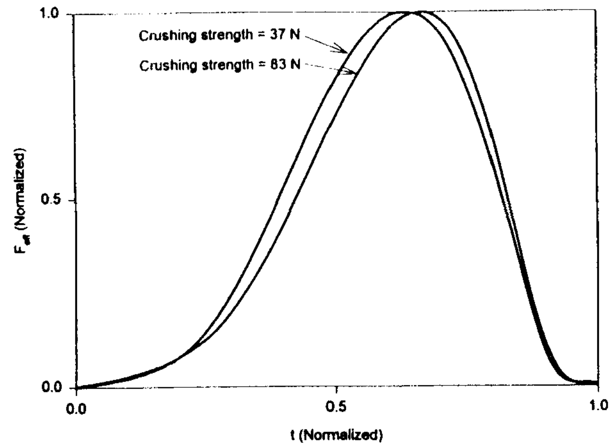

Figure 10. Normalized force–time profiles for tablets having different crushing strengths.

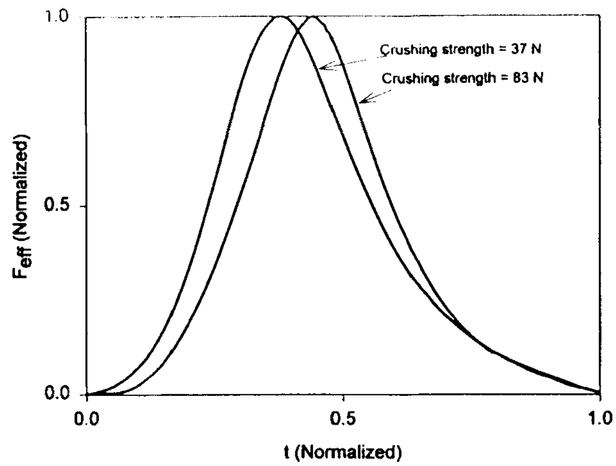

Figure 11. Normalized difference force–time profiles for tablets having different crushing strengths.

learning technique, may give promising possibilities (9,10).

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