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RESEARCH PAPER

A New Method to Evaluate the Elastic Behavior of Tablets During Compression

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ABSTRACT

A new method to evaluate elastic/plastic behavior of tablets from tablet compression force–time data is presented. Tablets were compressed in an instrumented eccentric single-punch tablet machine. Equations for the calculation of relative elasticity were derived for both upper and lower punch forces. The experimental work was based on a 3^2 design having binder solution amount and atomizing air pressure as independent variables. Multilinear stepwise regression analysis was applied in studying the effects of granulation variables. It was concluded that the relative elasticity of tablets is dependent on binder solution amount. Furthermore, this study showed that the relative elasticity parameters can be useful in quantification of elastic behavior of tablets.

INTRODUCTION

Tablet compression is a widely studied field in pharmaceutical technology (1–6). One important aim of these studies has been the classification of materials according to their compressional behavior. Materials are typically divided into two main categories, elastic and plastic. More generally materials are considered as viscoelastic systems (7). Another possibility for classification of the changes in materials under pressure is the division into reversible and irreversible. Reversible changes represent elastic behavior, and irreversible changes contain both the plastic nature of materials and their tendency to fragment during compression. In practice, the determination of the degree of elasticity, plasticity, or fragmentation has proved to be quite difficult (8–10).

This paper presents a method to evaluate elastic/plastic behavior of tablets from tablet compression force–time data. This method may be valuable in quantification of the degree of reversible and irreversible changes during tablet compression. The method was used to study the influence of granulation variables on the compressional behavior of tablets.

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THEORY

In an eccentric tablet machine the upper punch displacement is often almost symmetrical. As a first approximation it can be assumed that if an ideal rubber elastic material is compressed in an eccentric tablet machine, the force-time curve is also symmetrical in respect to the time point t_{max}, which is the time when the maximum upper punch force, $F_{up,max}$, is achieved (Fig. 1). If the consolidation force-time curve is reflected with the plane of t_{max}, a symmetrical decreasing force curve after t_{max} is achieved. This symmetrical curve represents a theoretical rubber elastic system (curve $F_{up,e}$). In practice, however, the force-time curves are always asymmetrical in respect to the time t_{max}. This is due to the irreversible deformation of materials under high pressure. A real force-time curve has the form of curve F_{up} in Fig. 1.

Area A1 in the Fig. 1 can be calculated as an integral of the force-time curve during the consolidation phase ($0 \le t \le t_{max}$):

$$A1 = \int_0^{t_{max}} F_{up} dt = \int_{t_{max}}^{2t_{max}} F_{up,e} dt \quad (1)$$

and area A2 as:

$$A2 = \int_{t_{max}}^{2t_{max}} F_{up} dt \quad (2)$$

In every case [Fig. 1(a)] the surface areas can be related to each other as:

$$A3 = A1 - A2 \quad (3)$$

Thus A3 can be calculated from integral:

$$A3 = \int_{t_{max}}^{2t_{max}} (F_{up,e} - F_{up}) dt \quad (4)$$

The difference ($F_{up,e} - F_{up}$) as a function of time is presented in Fig. 1(b). The time needed to achieve the maximum of this difference ($t_{max} + \Delta t$) may give information on the relative magnitude of plasticity and fragmentation of material, because plastic deformation is a slow and fragmentation a rapid phenomenon. The smaller the time Δt is, the more prominent is the effect of fragmentation. Also the height of the difference $F_{up,e} - F_{up}$ at time point ($t_{max} + \Delta t$) may be important. The higher values of the difference curve can be related obviously to fragmentation. For a totally fragmented material, for which $\Delta t = 0$, the height of the curve is actually the maximum compression force $F_{up,max}$.

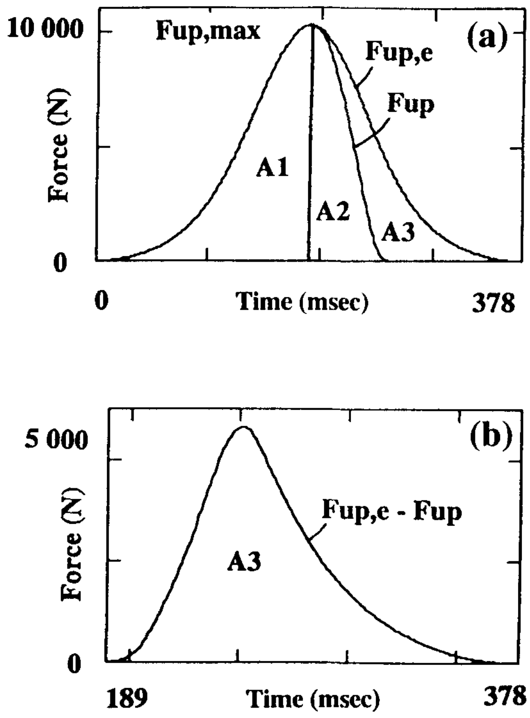

Figure 1. Definition of parameters.

Finally, we define relative elasticity measured from the upper force curve RE,F_{up} as follows:

$$RE,F_{up} = 1 - A3/A1 \quad \text{or}$$

$$RE,F_{up} = (1 - A3/A1)\ 100\% \quad (5)$$

Relative elasticity (RE,F_{up}) determined from the force-time data obtained from the upper punch can be used as a measure for relative elasticity for a material. For a totally elastic material this value will be 1 (or 100%) and for a system which undergoes entire irreversible deformation without any elastic behavior the ratio will be zero (or 0%). Real systems, however, are always between 0% and 100%.

The analogue parameters B1, B3, and relative elasticity (RE,F_{lp}) can be defined also for lower punch force. The relative elasticity (RE,F_{lp}) measured from lower force curve is thus:

$$RE,F_{lp} = 1 - B3/B1 \quad \text{or}$$

$$RE,F_{lp} = (1 - B3/B1)\ 100\% \quad (6)$$

The method described here makes it possible to classify materials according to their behavior under compression with direct numbers. The possible limitations of the method are the irreversible changes in materials which occur also during consolidation phase. Therefore, the upper force and lower force maxima and also the t_{max} values for force–time curves are in a certain respect theoretical. Determination of *RE* values requires an eccentric tablet machine or, more preferably, a compaction simulator in which the punch displacement can be adjusted symmetrically. The practical significance of the limitations and general applicability of the present method can be, however, confirmed experimentally.

MATERIALS AND METHODS

Materials

The filler material was 80-mesh α-lactose monohydrate (DMV, Veghel, Netherlands). Two percent of anhydrous theophylline (Ph. Eur.) was added as a marker drug in each batch to be granulated. Batches of 3 kg were granulated using 20% aqueous dispersion of polyvinylpyrrolidone (Kollidon® K25, BASF, Germany).

Preparation of Granules

The granules were produced in an automated fluidized-bed granulator using a 3^2 experimental factorial design. The atomizing air pressure (p) and binder solution amount (m) were used as independent variables. The atomizing air pressures were 1.0, 1.5, and 2.0 bar; and the binder solution amounts were 150, 300, and 450 g. A total of 12 batches, 9 experimental batches and 3 center point replicate batches, were granulated and tableted.

Tablet Compression

Tablets (target weight 335 mg) were compressed in an instrumented eccentric tablet machine (Korsch EK0, Erweka Apparatebau, Germany) using flat-faced punches with a diameter of 9 mm. Before the compression a sample of granules (400 g) was mixed for 5 min with 0.5% magnesium stearate (Ph. Eur.) in a Turbula mixer (System Schatz, Willy A. Bachhofen, Switzerland). The compression force was 10 kN. During the compression the upper and lower forces were measured in each batch from 10 tablets. The number of data points measured during a single compression cycle was about 400.

Because the directly measured force curve had some disturbing peaks, the curves were first smoothed using floating 5-point smoothing. This was especially important in order to determine more accurately the upper force maximum and the time at which the maximum was obtained. Thereafter the consolidation phase curve was reflected against the line at t_{max} and A1, A3, B1, B3, and ratios A3/A1 and B3/B1 were calculated. Also, images of the type shown in Fig. 1 were drawn. Furthermore the *R* values corresponding to the maximum compression force were determined.

Regression Analysis

Multilinear stepwise regression analysis was applied in studying the effects of granulation variables. Before statistical analysis the independent variables were normalized to −1, 0 and +1.

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

$$Y(p,m) = a_0 + a_1p + a_2m + a_3pm + a_4p^2 + a_5m^2 + a_6p^2m + a_7m^2p + a_8p^2m^2 \quad (7)$$

where $a_0, \ldots, a_8$ are the coefficients of a certain system. Symbols p and m denote the atomizing air pressure and binder solution amount, respectively.

The models were simplified by a normal stepwise technique. The additional terms were included in the models so that the squared multiple *R* increased as much as possible. The certainty of each term included in the models were tested with the *t* test. Only significant terms ($p < 0.05$) were included. Statistical analysis and the generation of the regression models were performed using SYSTAT v. 5.0 (SYSTAT Inc., USA).

RESULTS AND DISCUSSION

The upper compression force (F_{up}) varied from 9.76 to 10.3 kN, and the lower force (F_{lp}) from 8.95 to 9.59 kN (Table 1). This means that the compression pressure was in every case within the range 153.3–162.0 N/mm². The integral force–time curve for the upper (A1) punch during the consolidation phase ($0 \le t \le t_{max}$) ranged from 515.2 to 563.0 kN s and the integral A3 from 221.2 to 241.2 kN s, respectively. Furthermore, the 1 − (A3/A1) ratio was >0.5553 in every case. The analogue parameter 1 − (B3/B1) for the lower punch force was in every case systematically higher than the corresponding upper force parameter (Table 1).

Regression Models

The regression models (Table 2) for the upper force parameters [A3, A1, and 1 − (A3/A1)] show that the

Table 1

Compression Forces and Derived Compression Parameters of Tablets (p, Atomizing Air Pressure; m, Binder Solution Amount)

A. Upper Punch

p	m	F_{up} (kN)	A3 (kN sec)	A1 (kN sec)	1 - A3/A1
-1	-1	9.84	221.2	515.2	0.5707
-1	0	9.82	233.6	532.4	0.5610
-1	1	9.82	231.5	528.7	0.5622
0	-1	9.86	223.2	520.7	0.5713
0	0	10.1	230.8	543.4	0.5754
0	0	9.87	239.5	548.5	0.5634
0	0	10.2	237.2	563.0	0.5786
0	0	9.86	241.2	542.4	0.5553
0	1	10.1	231.9	547.5	0.5764
1	-1	10.3	222.9	540.8	0.5879
1	0	10.2	233.8	550.1	0.5750
1	1	9.76	229.2	530.9	0.5682

B. Lower Punch

p	m	F_{lp} (kN)	B3 (kN sec)	B1 (kN sec)	1 - B3/B1	$R = F_{lp}/F_{up}$
-1	-1	9.04	182.2	475.5	0.6168	0.919
-1	0	9.06	195.1	491.7	0.6031	0.923
-1	1	9.09	197.9	492.2	0.5979	0.925
0	-1	9.14	188.5	484.8	0.6113	0.928
0	0	9.47	203.4	515.2	0.6052	0.938
0	0	8.95	193.7	478.8	0.5953	0.907
0	0	9.44	206.9	511.9	0.5958	0.924
0	0	9.16	203.0	496.3	0.5910	0.929
0	1	9.43	205.2	518.3	0.6041	0.933
1	-1	9.59	193.3	510.1	0.6212	0.930
1	0	9.56	202.8	519.8	0.6099	0.934
1	1	9.12	200.3	499.9	0.5993	0.935

model of A3 (related to the irreversible deformation of the material) had the highest squared multiple R, being 0.813. This model had linear terms for atomizing air pressure and binder solution amount, and also a squared term for binder solution amount. The same parameters are seen also in the regression model of A1. In the case of parameter 1 - (A3/A1) the value of R^2 is quite low (0.431), indicating that the tablet compression hinders the effects of granulation process variables.

Regression models (Table 3) for lower punch parameters [B3, B1, and 1 - (B3/B1)] showed that the squared multiple R for B1 was the lowest (only 0.451) and the

Table 2

Regression Models and Corresponding Values of Squared Multiple R for the Upper Force Parameters A3, A1, and 1 - (A3/A1)

$A3 = 236 - 0.0667p + 4.22m - 9.37\ m^2$	$R^2 = 0.813$
$A1 = 547 + 7.59p + 5.07m - 16.0\ m^2$	$R^2 = 0.630$
$1 - (A3/A1) = 0.568 + 0.00620p - 0.00385m + 0.00467\ m^2$	$R^2 = 0.431$

Table 3

Regression Models and Corresponding Values of Squared Multiple R for the Lower Force Parameters B3, B1, and 1 - (B3/B1)

B3 = 201 + 3.53p + 6.57m - 6.25 m^2	R^2 = 0.750
B1 = 502 + 11.7p + 6.67m - 5.48 m^2	R^2 = 0.451
1 - (B3/B1) = 0.600 + 0.00210p - 0.00800m + 0.00838 m^2	R^2 = 0.675

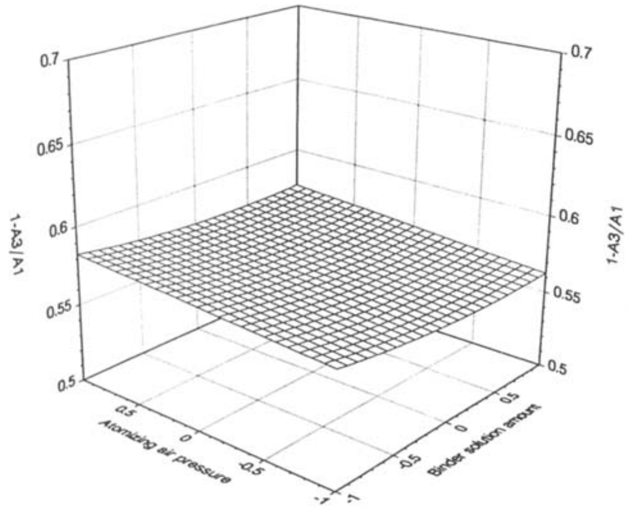

Figure 2. Area 1 - (A3/A1) as a function of atomizing air pressure and binder solution amount.

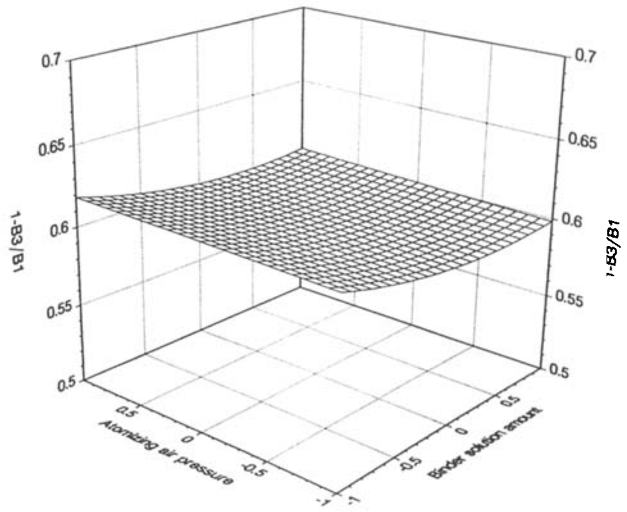

Figure 3. Area 1 - (B3/B1) as a function of atomizing air pressure and binder solution amount.

parameter B3 had the highest R^2 (0.750), which was quite similar to the corresponding parameter A3 in the upper punch.

The response surfaces for the relative elasticity parameters 1 - (A3/A1) and 1 - (B3/B1) are given in Figs. 2 and 3. These response surfaces in general are quite stable and have very similar structure. Both parameters are nonlinearly dependent on binder solution amount. The relative elasticities decrease as binder solution amount (and obviously the granule size) increases. Atomizing air pressure does not have any effect on relative elasticities. This is expected because the atomizing air pressure was not an accurate constant but changed in the range -20% to +20% around the preset target value.

CONCLUSIONS

On the basis of this study the following can be concluded:

- Relative elasticity of tablets is dependent on binder solution amount.
- The method can be useful in quantification of elastic behavior of tablets.

REFERENCES

1. K. Ridgway, E. Shotton, and J. Glasby, J. Pharm. Pharmac., 21(Suppl.), 19S (1969).
2. S. K. Dwivedi, R. J. Gates, and A. G. Mitchell, J. Pharm. Pharmacol., 44, 459 (1992).
3. J. S. M. Garr and M. H. Rubinstein, Int. J. Pharm., 82, 71 (1992).
4. P. J. Vogel, and P. C. Schmidt, Drug Dev. Ind. Pharm., 19(15), 1917 (1993).
5. S. Malamataris and J. E. Rees, Int. J. Pharm., 92, 123 (1993).
6. S. A. S. Aly, S.T.P. Pharma Sci., 3(3), 221 (1993).
7. D. W. Danielson, W. T. Morehead, and E. G. Rippe, J. Pharm. Sci., 72(4), 342 (1983).

8. P. J. Vogel and P. C. Schmidt, Drug. Dev. Ind. Pharm., 19(5), 1917 (1993).
9. P. C. Schmidt and P. J. Vogel, Drug. Dev. Ind. Pharm., 20(5), 921 (1994).
10. R. Martinez-Pacheco, J. L. Villa-Jatao, C. Souto, and J. L. Cómez-Amoza, Drug. Dev. Ind. Pharm., 16(2), 231 (1990).