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RESEARCH PAPER

A New Method to Evaluate the Consolidation Behavior of Pharmaceutical Materials by Using the Fraser–Suzuki Function

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ABSTRACT

A new method was developed to evaluate the consolidation behavior of different pharmaceutical materials. A method to evaluate the elastic deformation of the different parts of the tablet machine is described. The used model is based on the Fraser–Suzuki function, which was modified to fit the force-time course. This function has three parameters, which describe the consolidation behaviour of pharmaceutical materials. Parameter A (form of the increasing part of the force-time course) and tr *parameter (time of force maximum) give qualitative evaluation of the irreversible deformation during the compression process. Parameter S (form of the decreasing part of the curve) describes the decompression phase and provides information about the elastic behaviour of the compressed material. In this article, the importance of the different parameters is presented. The applicability of this function to different kinds of ethylcellulose is also presented.*

Key Words: *Consolidation behavior; Elastic deformation; Ethylcellulose; Tablet.*

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INTRODUCTION AND INTELLECTUAL APPROACH FOR THE METHOD

It is known that the compression process can be described by using static and dynamic models. In the case of static models (1–5), time is not considered, although it is a very important factor in the deformation process. The viscoelastic reactions are time dependent, especially for the plastic flow (6–9).

Many methods have been used for the parameterization of force-time profiles in tableting. Some of them were applied on the eccentric tablet machines (6,10,11) and others on the rotary tablet machines (12,13). These methods gave a qualitative evaluation for the tableting behaviour of pharmaceutical materials.

Despite extensive research in this field, it was so far impossible to evaluate the irreversible and reversible deformation during compaction by using some basic parameters. For this aim we used the modified Fraser–Suzuki function as a fitting function for force-time course, thus being able to describe the deformation behaviour of the material during compression. Before we explain this function, the intellectual approach for using it should be outlined. For compressing a tablet to a defined hardness, respectively porosity, a defined compression force must be applied. The compression force depends on different factors. First, by compressing a constant powder weight, a variation in the applied force causes a change in the measured force. The second important factor is the substance itself. If it has good compressibility, the necessary force will be low. The reasons can be the crystallographic and thermodynamic properties of the material. Crystals with a large lattice energy will show a higher resistance against consolidation. The tabletting properties of the material also depends on their deformation behaviour. The known extreme cases are as follows. For elastic bodies, the force applied to consolidate them will be fully given back (Actio = Reactio). This is expressed as a completely elastic deformation. For plastic bodies, the force applied will be saved as energy in the body and express no elastic deformation at all. During tablet building, these two processes never occur alone but only in combination.

We asked which parameter can draw a conclusion about the deformation behaviour during compression? It is known that during the compression process of a tablet, the force-time course is substance dependent (Fig. 1). The steepness of the curve increase gives information about the force transmission in powder and how fast the substance is able to give way to the force applied (e.g., if the substance is able to give way quickly to the influence of the applied force, this is expressed by a flat curve increase). The time of the force maximum gives information about the irreversible deformation of the material. The curve decrease gives information about the decompression phase, respectively, the elastic deformation of the material.

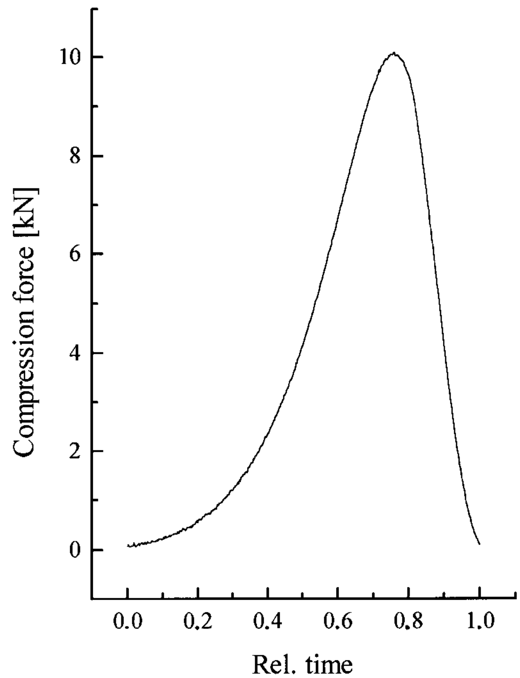


Figure 1. Force-time curve course.

MATERIALS AND METHODS

Materials

Three types of ethylcellulose with different molecular weights (i.e., different viscosity grades: 7, 22, 50 cP) were used. They were gifts from Hercules Aqualon (Darmstadt, Germany) and have an ethoxyl content of 48.0–49.5%.

Experimental

Tablets were manufactured by direct compression using instrumented eccentric tablet press EK-0 DMS (Korsch, Berlin, Germany) connected to an amplifier (HBM Company, Darmstadt, Germany) of the DMS-plus type with a frequency carrier strength of 4.8 kHz. The material was compressed with flat circular punches of 9 mm diameter at a rate of 10 tablets/min. The tablet machine is instrumented with a strain cage to measure the compression force of the upper and lower punches. The displacement of the upper punch was also measured by using an inductive displacement measure. The materials were compressed to different porosities by reaching the maximum of the displacement; therefore, it is very important to evaluate the elastic deformation of the punches and the tablet machine during the compression cycle.

The force-time data were recorded when the upper punch force was ≥50 N. The fitting was done using Microcal Origin, version 3.54 (Microcal Software Inc.).

Evaluation of the Elastic Deformation Factors

The measured displacement of the upper punch was not exactly correct because the elastic deformation factors of the different parts of the tablet machine cannot be detected from the displacement sensor. These factors should be evaluated to measure the correct displacement value.

By pressing punch on punch, the total elastic deformation (E. def.$_{(\text{entire})}$) results from the elastic deformation of the upper punch, lower punch, and the tablet machine (Fig. 2). For this reason it is necessary to measure the individual elastic deformation of the tablet machine and

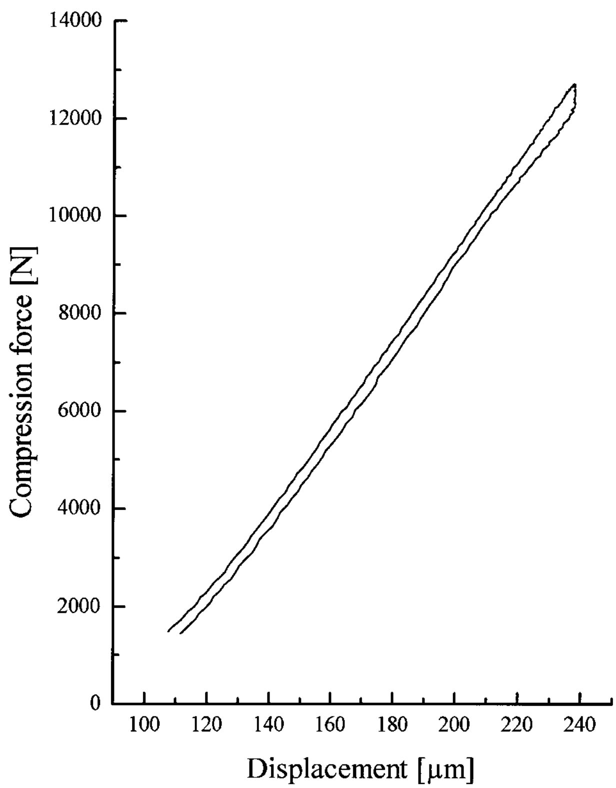


Figure 2. Compression force-displacement curve by punch-on-punch pressing.

the punches, which normally have different forces during the compression cycle.

Figure 2 shows a hysteresis course and the linear correlation between the elastic deformation and the force above 1500 N. This phenomenon was discussed before by many authors (14–17) who declared it was the result of the tilt behaviour of the upper punch. The slope of the linear part of the curve was determined by linear regression. For the measurement of the individual elastic deformation of the punches, we used steel punches with a radius of 38 mm. The elastic deformation of the steel punches was ignored, comparing them with the elastic deformation of the used punches (radius 9 mm). The measured elastic deformation of the individual punches are a result of the elastic deformation of the punches and the eccentric press machine:

$$\begin{aligned}
\text{Elastic deformation}_{(\text{measured upper punch})} &= \text{E. def.}_{(\text{upper punch})} + \text{E. def.}_{(\text{press machine})}\\
\text{Elastic deformation}_{(\text{measured lower punch})} &= \text{E. def.}_{(\text{lower punch})} + \text{E. def.}_{(\text{press machine})}\\
\text{Elastic deformation}_{(\text{measured press machine})} &= \text{E. def.}_{(\text{press machine})} + \text{E. def.}_{(\text{unknown})}\\
\text{Elastic deformation}_{(\text{measured result})} &= \text{E. def.}_{(\text{upper punch})} + \text{E. def.}_{(\text{lower punch})} + \text{E. def.}_{(\text{press machine})}\\
\text{Elastic deformation}_{(\text{measured upper punch})} &= 09.676\ \mu\text{m/kN}\\
\text{Elastic deformation}_{(\text{measured lower punch})} &= 10.927\ \mu\text{m/kN}\\
\text{Elastic deformation}_{(\text{measured press machine})} &= 07.910\ \mu\text{m/kN}\\
\text{Elastic deformation}_{(\text{measured result})} &= 12.693\ \mu\text{m/kN}\\
\text{Elastic deformation}_{(\text{entire})} &= 12.544\ \mu\text{m/kN}
\end{aligned}$$

By comparing the elastic deformation$_{(\text{entire})}$ with the elastic deformation$_{(\text{measured result})}$, a difference of only 0.149 μm/kN or 1.96% can be found, which has been accepted. The proportion of the elastic deformation distribution can be calculated using the measured data. The upper punch received 5.892 μm/kN or 46.97%, and the lower punch received 6.652 μm/kN or 53.03%. The corrected displacement data of the upper punch were calculated using Eq. (1):

$$CDD = RDD - \{[\text{E. def.}_{(\text{upper punch})} \times upf] + [\text{E. def.}_{(\text{lower punch})} \times lpf]\} \quad (1)$$

where *CDD* is the corrected displacement data, *RDD* is the recorded displacement data, E. def. is the elastic deformation, *upf* is the upper punch force, and *lpf*, the lower punch force. In Fig. 3 the difference between

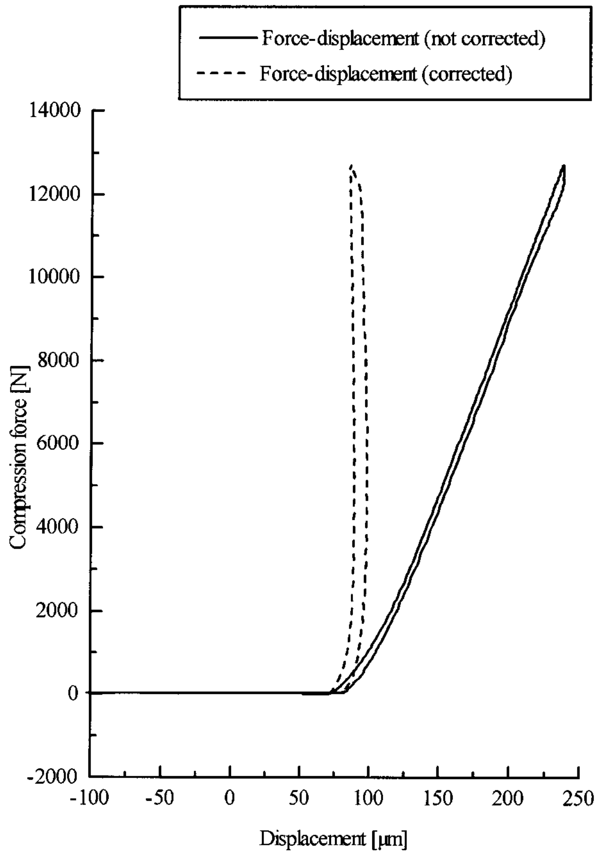


Figure 3. Compression force-corrected and uncorrected displacement curve.

the corrected and uncorrected displacement data can be seen. The data were regarded during punch-on-punch pressing.

RESULTS AND DISCUSSION

Fraser–Suzuki Function

The Fraser–Suzuki function [Eq. (2)] is an exponential function (18) and the result of the linear combination of the Gauss and Cauchy function (19). This function was used originally to evaluate chromatographic signals (20).

$$f(t) = H \times \left\{ \left[\frac{-(\ln 2)}{A^2} \right] \times \left[\ln \left(\frac{[1 + A \times (t - tr)]}{S} \right) \times (2 \ln 2)^{1/2} \right\} \tag{2}$$

where H is the peak maximum, A is the asymmetry factor, tr is the time by force maximum, and S is the standard deviation of the peak.

We modified this equation to use it as a fitting function for the force-time course:

$$f(t) = H \times \left\{ \left[\frac{-0.693}{A^2} \right] \times \left[\ln \left(\frac{\{1 + A \times (tr - t)\}}{S} \right) \times 1.177 \right]^2 \right\} \tag{3}$$

The Evaluated Parameter

First, we show how a variation of the mentioned parameters affects the curve course. In Fig. 4, curve courses with constant S parameter = 0.250, constant tr parameter = 0.810, and varying A parameter are shown. An increase in the A parameter causes a change in the width of the increasing side of the curve (Fig. 4). The curve increase gives information about the force transformation between the particles and how fast the particles are able to make way to the compression force influence. This

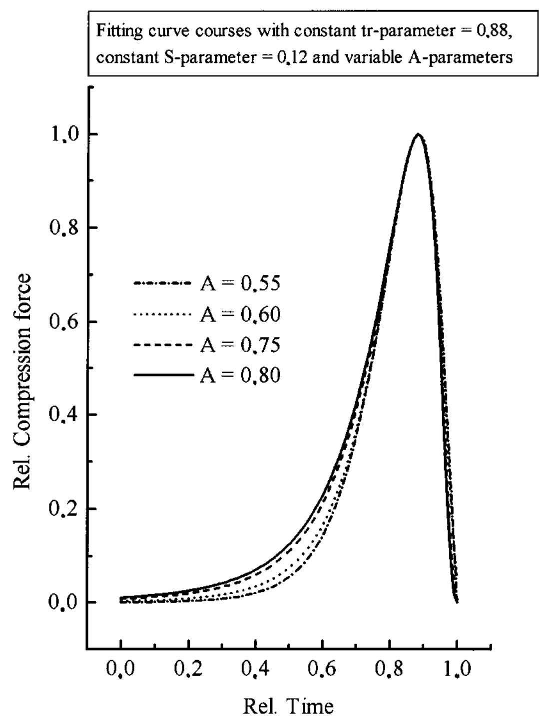


Figure 4. Fitting function curve courses by increasing the A parameter.

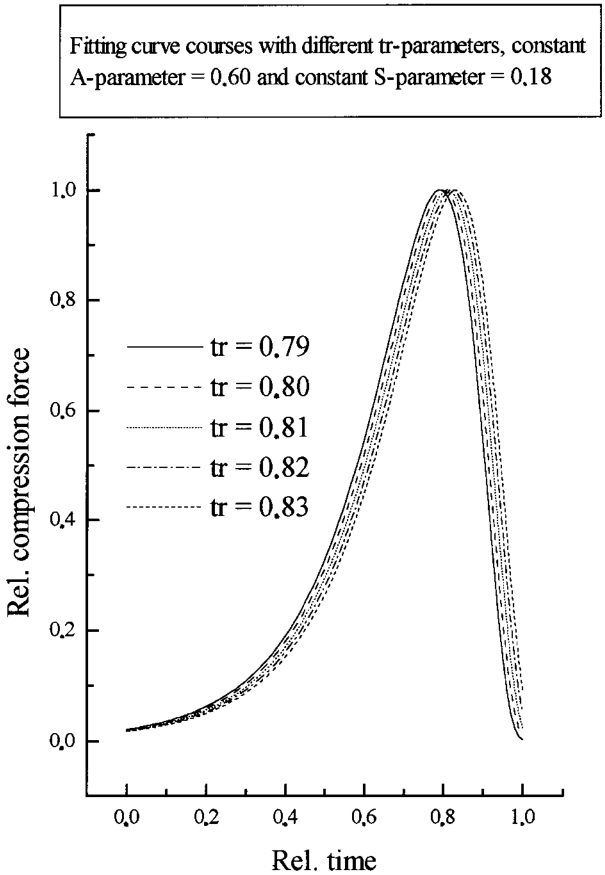


Figure 5. Fitting curve courses by increasing the *tr* parameter.

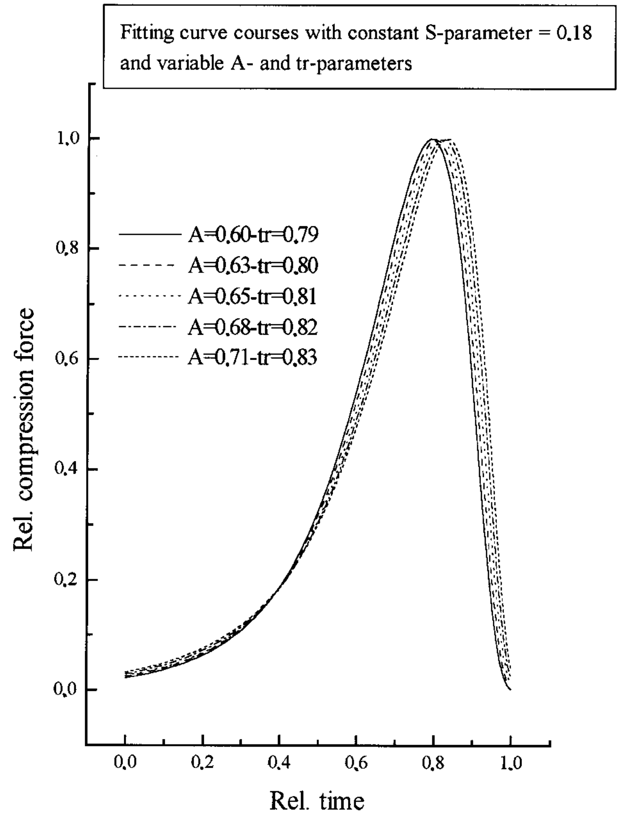


Figure 6. Fitting curve courses by increasing the A and *tr* parameters.

means mostly that the higher the A parameter, the bigger the irreversible deformation part.

The decreasing part of the curve describes the relief phase or the decompression phase of the compression cycle. It gives information about the elastic deformation of the material. The increase of the *tr* value (Fig. 5) leads to parallel postponement of the curve. This means that the maximal resistance against consolidation will be reached later and a higher irreversible deformation can be predicted, which can be fragmentation or plastic deformation.

Both parameter A and parameter *tr* should be considered to evaluate the irreversible deformation. Figure 6 shows fitting curve courses with constant S parameter and variable A and *tr* parameters. The curve course with A parameter = 0.71 and *tr* parameter = 0.83 is a curve course with developed irreversible deformation. An increase in S value, which can describe the decreasing part of the curve (Fig. 7), causes smaller differences between the increase and the decrease curve; therefore, a higher elastic deformation can be predicted.

In Fig. 8, the goodness of fit by the Fraser–Suzuki function can be seen. Chi squared was used as a measure of the fitting goodness.

Investigation of the Consolidation Behaviour of Ethylcellulose with Different Molecular Weights

Ethylcellulose has been investigated often (21–23). Two different ethylcelluloses with different molecular weights (i.e., different viscosity grades of 5% polymer solution) were investigated: ethylcellulose 7 cP and 50 cP. The different ethylcelluloses were compressed to different compression forces. In Tables 1 and 2, the function parameters A, *tr*, and S are listed. The A and *tr* parameters decrease with increasing compression force. This shows that the irreversible deformation decreases with increasing the compression force. The S parameter

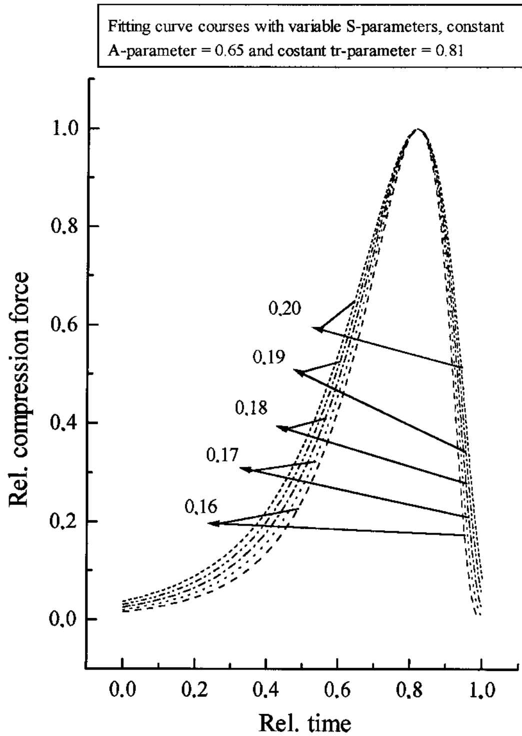


Figure 7. Fitting function curve courses by increasing the S parameter.

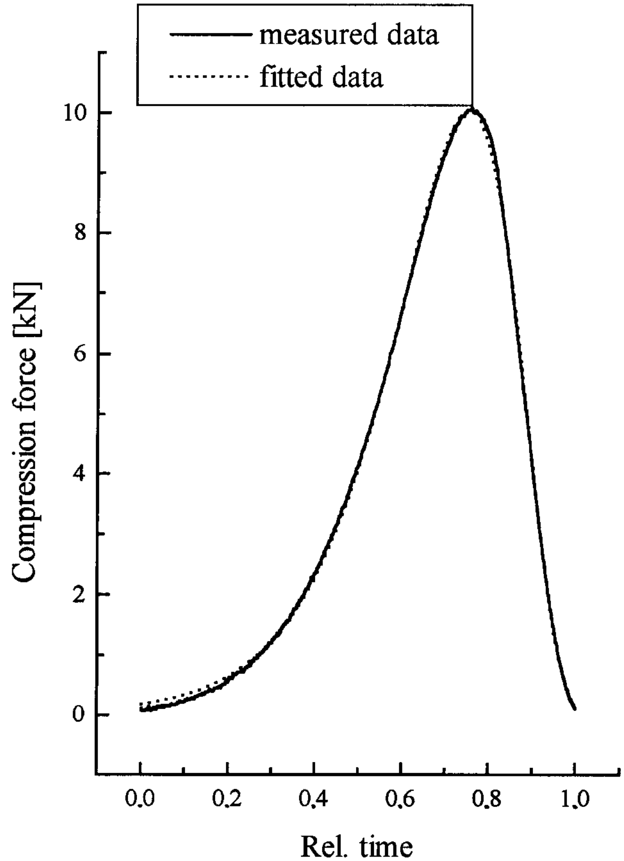


Figure 8. The goodness of the fitting function.

Table 1

Parameters of the Modified Fraser–Suzuki Function for Ethylcellulose 50 cP Compressed to Different Compression Forces

Compression Force	A Parameter	*tr* Parameter	S Parameter
2.247 ± 0.0449	0.556 ± 0.0033	0.739 ± 0.0021	0.343 ± 0.0031
5.053 ± 0.0671	0.572 ± 0.0036	0.767 ± 0.0065	0.288 ± 0.0013
7.258 ± 0.0756	0.549 ± 0.0041	0.773 ± 0.0023	0.266 ± 0.0014
10.581 ± 0.0245	0.495 ± 0.0023	0.774 ± 0.0016	0.252 ± 0.0020
11.892 ± 0.0848	0.464 ± 0.0027	0.782 ± 0.0032	0.253 ± 0.0009
15.096 ± 0.1878	0.405 ± 0.0032	0.782 ± 0.0013	0.259 ± 0.0009

Values are means ± SD.

Table 2

Parameters of the Modified Fraser–Suzuki Function for Ethylcellulose 7 cP Compressed to Different Compression Forces

Compression Force	A Parameter	*tr* Parameter	S Parameter
2.242 ± 0.0203	0.529 ± 0.0098	0.718 ± 0.0018	0.377 ± 0.0033
5.229 ± 0.0882	0.565 ± 0.0070	0.754 ± 0.0013	0.318 ± 0.0014
7.060 ± 0.0592	0.551 ± 0.0056	0.761 ± 0.0026	0.303 ± 0.0014
10.243 ± 0.0788	0.505 ± 0.0035	0.742 ± 0.0021	0.276 ± 0.0017
12.059 ± 0.1022	0.477 ± 0.0045	0.778 ± 0.0014	0.259 ± 0.0012
15.207 ± 0.1319	0.414 ± 0.0035	0.773 ± 0.0031	0.283 ± 0.0017

Values are means ± SD.

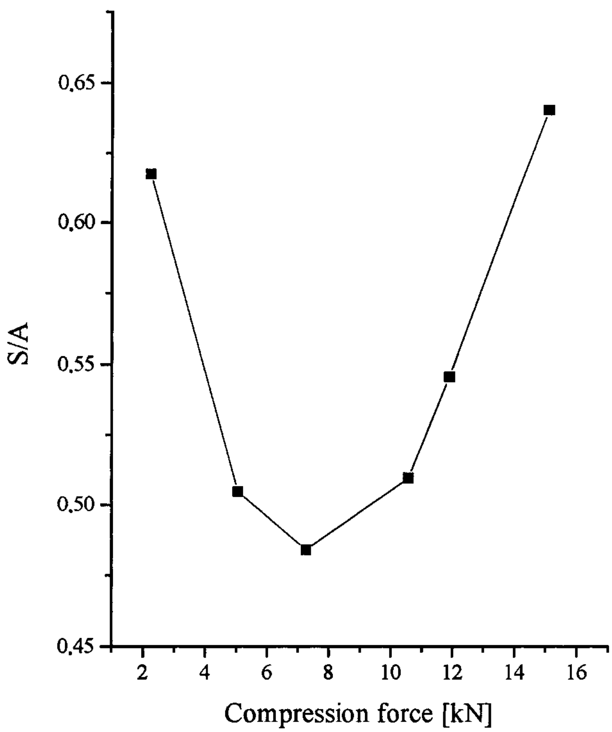


Figure 9. The relation between the S and A parameters by different compression forces.

decreases also by increasing the compression force. This also means that the reversible deformation relatively decreases by increasing the compression force. The relation between the S and A parameter can be used to evaluate the relation between reversible and irreversible deformation during the compression process. Figure 9 shows the relation between reversible and irreversible deformation by a compression force of 7 kN, which is very desirable because the relation between reversible and irreversible deformation has the minimum value.

To investigate the consolidation behaviour of different materials, they should be compressed using the same porosity instead of using the same compression force, because the porosity is more important for the compression process than the compression force (24,25). Table 3 shows the function parameters for different ethylcelluloses that were compressed to a porosity of 85%.

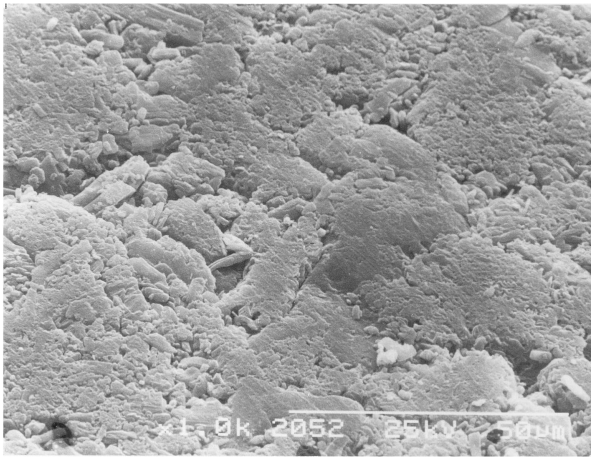
A distinctive or a developed irreversible deformation of the ethylcelluloses with low molecular weight can be predicted from the A and *tr* parameters in Table 3. To support this result we took an electron microscope picture. In Fig. 10, the surface of two ethylcelluloses, 7 cP and 50 cP, compressed to the same porosity, is shown. A developed fragmentation process of ethylcellulose 7 cP can be clearly seen. This can explain the better compressibility and compactibility of ethylcellulose with the lower molecular weight. The same results, including

Table 3

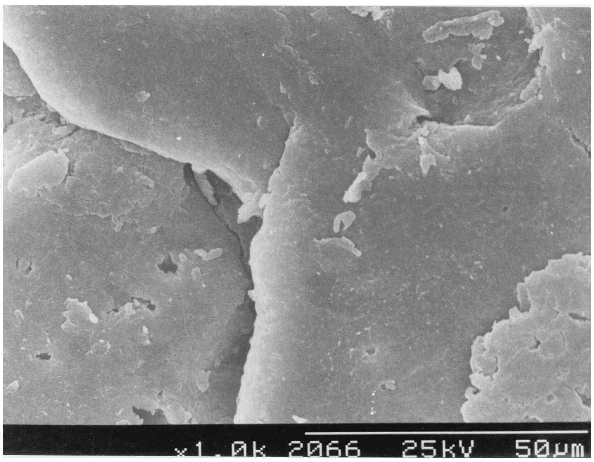
Parameters of the Modified Fraser–Suzuki Function of Different Ethylcelluloses Compressed to the Same Porosity 80%

Ethylcellulose (EC)	A Parameter	*tr* Parameter	S Parameter
EC 7cP	0.612 ± 0.0041	0.769 ± 0.0052	0.343 ± 0.0031
EC 22cP	0.593 ± 0.0036	0.746 ± 0.0036	0.288 ± 0.0014
EC 50cP	0.559 ± 0.0034	0.733 ± 0.0072	0.266 ± 0.0014

Values are means ± SD.



(a)



(b)

Figure 10. The tablet surface of two ethylcelluloses: (a) ethylcellulose 7 cP and (b) ethylcellulose 50 cP.

compactibility and compressibility, were found using another traditional method, ther Heckel plot and the plasticity value of Stamm and Mathes (21).

CONCLUSIONS

The modified Fraser–Suzuki function can be used as a fitting function for the force-time course to evaluate the consolidation behaviour of different pharmaceutical excipients. The A and *tr* parameters can give information about the irreversible deformation during the compression process and the S parameter information about the reversible deformation.

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