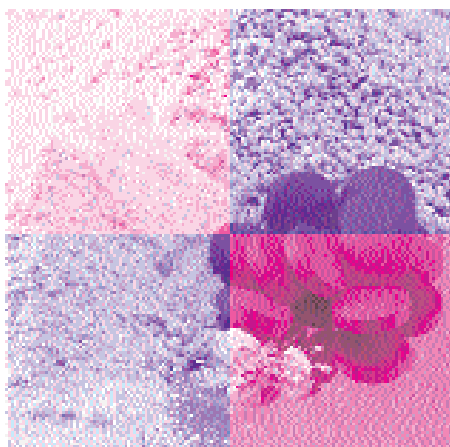


Evaluating the Elastic Behavior of Pharmaceutical Excipients and Binary Mixtures Using the Modified Fraser-Suzuki Function

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The individual compression behavior of microcrystalline cellulose, starch, dicalcium phosphate dihydrate, and ethylcellulose with different molecular weights was investigated using the modified Fraser-Suzuki function. The evaluated S-parameter of this function correlated with Young's modulus and was measured and evaluated during compression. The elastic behavior of three binary mixtures was also determined. Additionally, a qualitative and quantitative evaluation of the interaction in binary systems during compression was performed using the linear regression of the normalized S-parameter versus the volume of one component of the binary mixture.

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Many methods have been used to investigate the compression behavior of pharmaceutical excipients. For example, the Heckel plot, which describes the relationship between the porosity of the formulation and the compression pressure, is the most popular technique (1,2). It has also been used to investigate the decompression phase, that is, elastic recovery (3).

Previously, Leuenberger measured Brinell hardness and defined it as a compressibility parameter (4). However, this one point measurement does not allow a time-dependent consolidation course to be followed. Time is an important factor during the deformation of many pharmaceutical materials and therefore should be considered during an investigation of the deformation behavior. Rees and Rue previously investigated time-dependent deformation behavior by measuring the relaxation properties of produced tablets within a fixed time period (5). Later, Rippie and Danielson investigated the time-dependent elastic recovery following the compression cycle (6), and Emschermann and Müller divided the normalized force–time curve into two sections—a force increase section and a force decrease section—and the area under the curve was

evaluated, and the ratio between the two areas was calculated and used as a compressibility parameter (7). The energy distribution of the force displacement curve was used to evaluate the effective energy and the recovery energy (8,9).

The modified Weibull function considers the time-dependent pressure changes during the compression cycle (10,11). This function is used as a fitting function for the normalized force time and delivers three parameters, thereby enabling a qualitative evaluation of the reversible and irreversible deformation. Thus, a three-dimensional model was developed, which allows a qualitative evaluation of compressibility (12).

$$f(t) = H \times \exp \left\{ \left[\frac{-0.693}{A^2} \right] \times \left[\ln \left(\frac{1 + A \times (t - t_r)}{S} \right) \right]^2 \right\} \quad [1]$$

The modified Fraser-Suzuki function has been described previously (13). This function (see Equation 1) can be used to fit the force–time curve and describe the consolidation behavior of pharmaceutical substances (in which *H* is the compression force maximum, *A* and *t_r* provide information regarding irreversible deformation, and the *S*-parameter gives information concerning reversible deformation). In Figure 1, the goodness-of-fit function for the compression of ethylcellulose (EC) is shown.

In a previous study, the authors postulated a correlation between elastic behavior and the *S*-parameter of the modified Fraser-Suzuki function (13). The aim of this study was to find a measurable variable of elasticity that can be compared with the *S*-parameter. Furthermore, the applicability of the modified Fraser-Suzuki function to evaluate the compressibility of binary mixtures will also be presented and discussed.

Materials and methods

Materials. Table I shows the materials used and the suppliers.

Methods. True density. The true density of the materials used was determined (*n* = 5) using an Accupyc 1330 Pycnometer (Micromeritics Instrument Corp., Norcross, GA).

Mixing. The different mixtures were mixed for 10 min using a Cubic mixer KB 15 (Erweka Apparatebau GmbH, Heusenstamm, Germany).

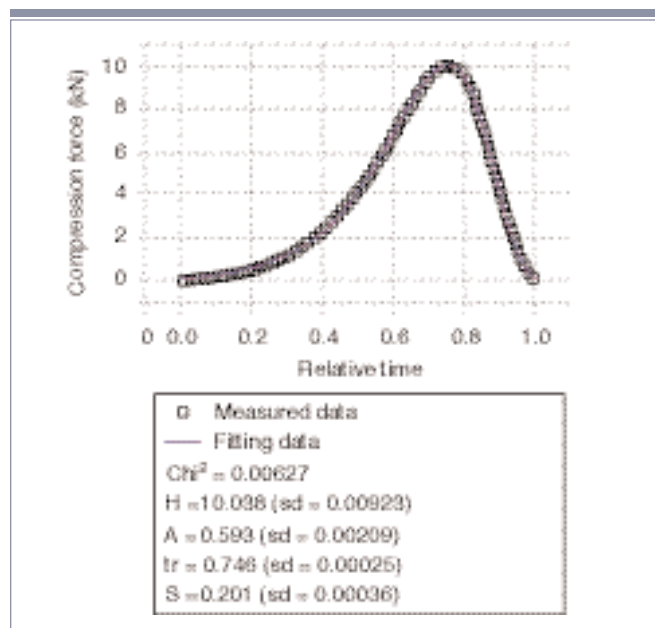


Figure 1: The goodness-of-fit function for the compression of ethylcellulose 22cP.

Tableting. An instrumented single-punch machine was used (EK0/DMS No. 1.0083.92; Korsch GmbH, Berlin, Germany). The upper-punch and lower-punch forces were measured, and the displacement of the upper punch was measured using an inductive transducer (W20 TK; Höttinger Baldwin Meßtechnik GmbH, Darmstadt, Germany). The elastic deformation of the punches and tableting machine during compression was measured and evaluated. Details of the evaluation have been previously published (13). The calibration of the transducer was performed using steel slip gauges of 2-, 3-, 4-, and 5-mm height. The tableting machine was connected to a DMC-plus amplifier (Höttinger Baldwin Meßtechnik GmbH) with a frequency carrier of 4.8 kHz.

The materials were compressed to different porosities with flat circular punches of 9-mm diameter at a rate of 10 tablets/min. Five tablets were produced at each condition. Equation 2 was used to evaluate the porosity.

Table I: The investigated materials and their producer/supplier.

Excipient	Brand Name	Producer/Supplier	Lot No.
Ethylcellulose 7cP	Ethocel	Hercules-Aqualon (Darmstadt, Germany)	10058
Ethylcellulose 22cP	Ethocel	Hercules-Aqualon (Darmstadt, Germany)	11069
Ethylcellulose 50cP	Ethocel	Hercules-Aqualon (Darmstadt, Germany)	10580
Microcrystalline cellulose	Avicel PH 102	Lehmann & Voss & Co.	M316C
Dicalcium phosphate dihydrate (CaHPO ₄ •2 H ₂ O)	Bekapress D2	BK (Ladenburg, Germany)	B. 27111/75132230
Polyethylene glycol 6000	PEG 6000	SERVA GmbH & Co. (Heidelberg, Germany)	16032
Potato starch	Potato starch	Caesar & Loretz GmbH (Hilden, Germany)	B. 96811

$$\text{Porosity} = \left(1 - \frac{\rho_{\text{bulk}}}{\rho_{\text{true}}}\right) \times 100 \quad [2]$$

where

ρ_{bulk} = tablet bulk density

ρ_{true} = true density of the compressed material

Tablet dimensions. The thickness, height, and diameter of the produced tablets ($n = 5$) were measured using a digital micrometer screw 18E (Mitutoyo, Kanagawa, Japan).

Results and discussion

Evaluating Young's modulus during compression. Several methods were used to evaluate elasticity (14,15). One problem when using these methods is the porosity-dependent Young's modulus, which often causes an error during the evaluation. The variation level of the measured value was high, even when using the same evaluation method. For example, the Young's modulus of microcrystalline cellulose (MCC) was found to vary between 0.0103 and 13 Gpa (16). For these reasons, the method of Laich et al. was used to evaluate Young's modulus, which enabled evaluation during the compression process (17). The basis of this method is Hooke's equation (see Equation 3) (18–19).

$$E = \frac{l}{\Delta l} \times \frac{F}{A} \quad [3]$$

where

Δl = alteration of length

l = length without load

E = Young's modulus

F = force

A = cross-sectional area

By using Sprigg's equation (see Equation 4), a correction of Young's modulus for porosity could be made and thus a correlation with the tablet compression cycle became possible (20). The porosity of the tablet during compression can be evaluated using Equation 5, and this was modified to make it measurable during the compression cycle. Equation 6 can be obtained by replacing Young's modulus and the porosity of Equation 4 with those in Equations 3 and 5. By using this equation, the Young's modulus during compression was evaluated (17). All parameters in this equation were available during the compression cycle by using the instrumented tablet machine.

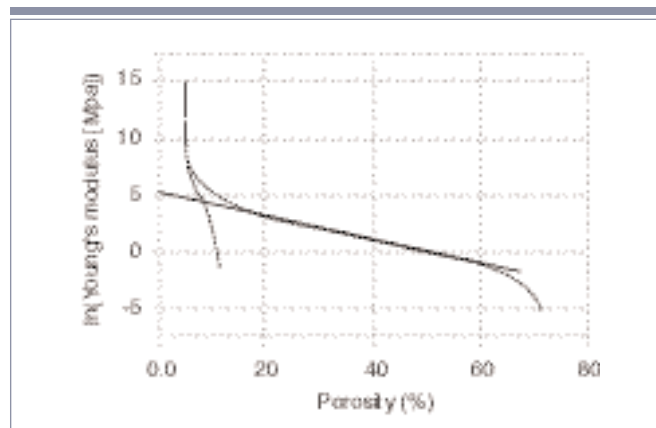


Figure 2: Young's modulus according to Equation 4.

$$\ln(E_c) = -k \times x + \ln(E_0) \quad [4]$$

where

E_c = Young's modulus for $x \neq 0$

E_0 = Young's modulus $x = 0$

x = porosity

k = constant

$$x = 1 - \frac{\rho_{\text{bulk}}}{\rho_{\text{true}}} = 1 - \frac{V_{\text{bulk}}}{V_{\text{true}}} = 1 - \frac{V_{\text{true}}}{\pi \times r^2 \times \Delta d} = 1 - \frac{m}{\pi \times r^2 \times \rho_{\text{true}} \times \Delta d} \quad [5]$$

where

m = mass of the powder or tablet

ρ_{true} = true density

ρ_{bulk} = bulk density

V_{true} = true volume

V_{bulk} = bulk volume

Δd = distance between upper and lower punch during the compression cycle (tablet thickness)

r = radius of the die

Plotting the natural logarithm of Young's modulus versus the porosity for the compression of the tablet showed good linearity in a defined range, with a correlation coefficient of $R = 0.9992$. The linear offset was evaluated by a linear fitting of the plot using 1200 pair values (see Figure 2). The Fraser-Suzuki function of different materials with different deformation be-

Table II. The evaluated parameters with standard deviation (sd) of the Fraser-Suzuki function for MCC using Avicel PH 102 compressed to various porosities ($n = 5$).

A-parameter/sd	S-parameter/sd	tr-parameter/sd	Porosity (%)/sd
0.625 ± 0.003	0.171 ± 0.0001	0.810 ± 0.001	30 ± 0.05
0.638 ± 0.004	0.169 ± 0.0001	0.813 ± 0.001	25 ± 0.02
0.646 ± 0.002	0.168 ± 0.0006	0.814 ± 0.003	20 ± 0.03
0.654 ± 0.006	0.167 ± 0.0007	0.816 ± 0.001	15 ± 0.04
0.660 ± 0.001	0.166 ± 0.0004	0.818 ± 0.002	10 ± 0.02

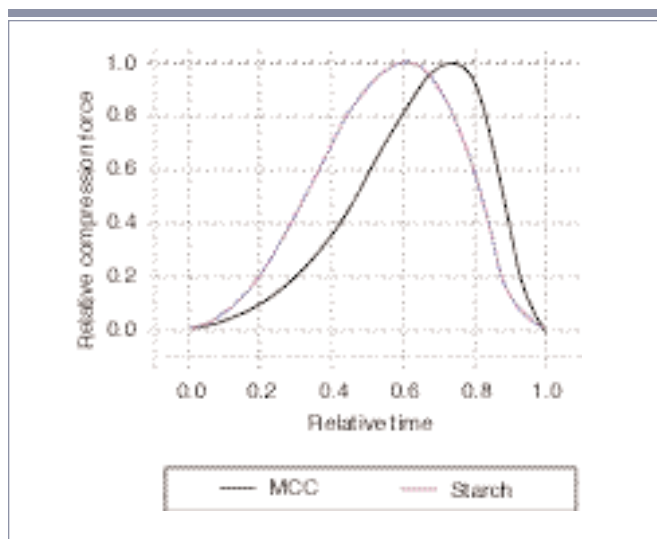


Figure 3: Force–time curves of MCC and starch during compression to a porosity of 30%.

havior was evaluated and compared with the obtained Young's modulus calculated according to Equation 6.

$$\ln\left(\frac{l \times F_{up}}{\Delta l \times A}\right) = -k \times \left(1 - \frac{m}{\pi \times r^2 \times \rho_{true} \times \Delta d}\right) + \ln(E_0) \quad [6]$$

where

l = thickness of the produced tablet at the end of compression (that is, at minimal detectable compression force F_{min})

Δl = thickness changes (movement of punches; absolute value)

F_{up} = force of upper punch

A = punch surface area ($\pi \times r^2$)

r = radius of the die

ρ_{true} = true density of the powder

m = tablet mass

Δd = distance between upper and lower punch during the compression cycle (tablet thickness)

k = constant (slope)

E_0 = Young's modulus for porosity = 0

Compression of Avicel PH 102. During compression of MCC, the values of A and tr were increased by raising the compression force or ramming (i.e., decreasing the end porosity of the produced tablet). Thus, the plastic deformation increased by raising the compression force, and the deformation energy transferred mostly to irreversible deformation. The S-parameter decreased when the compression force increased (see Table II). Because of the dominance of plastic deformation, MCC has a minimal tendency to reversible deformation behavior.

Compression of starch. The low A and tr parameters and the high S-parameter point to a slight irreversible deformation of starch (see Table III). The substance showed resistance to consolidation, which is reflected in the force–time curve. The starch curve shows that because of the high resistance to consolidation, the force increases faster than during MCC compression (see Figure 3). Thus, during starch compression, the time taken

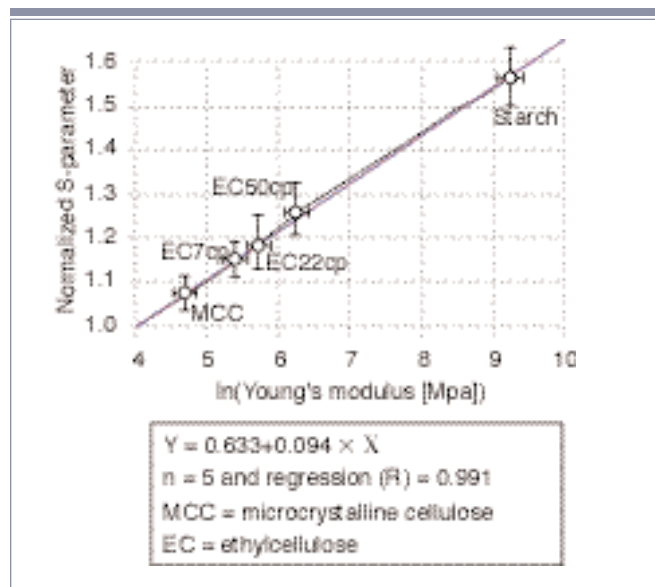


Figure 4: Normalized S-parameter versus ln(Young's modulus) of the investigated materials.

to reach the maximum force is less than during MCC compression. The slope of the force increases. One part of the curve will be high; the time to reach the force maximum will be short. This leads to lower A and tr parameters and a higher S-parameter compared with MCC.

Table III shows that the A and tr parameters increase and the S-parameter decreases by reducing the porosity of the produced tablets. This means that the extent of the irreversible deformation increases by raising the degree of ramming (decreasing the porosity). This behavior fits the results of a previous study (21).

Compression of ethylcellulose with different molecular weight.

Previous studies have presented and discussed the compression behavior of EC with different molecular weights (13,22). Here, the EC samples were compressed to the same porosity. The evaluated parameters of the Fraser-Suzuki function show that the different EC types have different compressibility values (see Table IV).

As the molecular weight increased, the S-parameter also increased. However, the A and tr parameters decreased. This means that the irreversible deformation of EC has an indirect proportional relationship to the molecular weight. The higher S-parameter is evidence of the higher elastic deformation properties of EC with high molecular weight. This result has also been confirmed using thermal mechanical analysis (23).

Elastic behavior of the different excipients

For the excipients investigated so far, Young's modulus was evaluated using Equation 6. The S-parameter was normalized using Equation 7. The natural logarithm of the Young's modulus values of the investigated materials was plotted against the normalized S-parameter. In Figure 4 the linear correlation between the mentioned parameters can be seen ($R^2 = 0.982$). The elasticity sequences of the investigated materials fit with previous investigations (24,25). These results confirm the supposition that the S-parameter of the modified Fraser-Suzuki function correlates with the elastic behavior of the investigated materials.

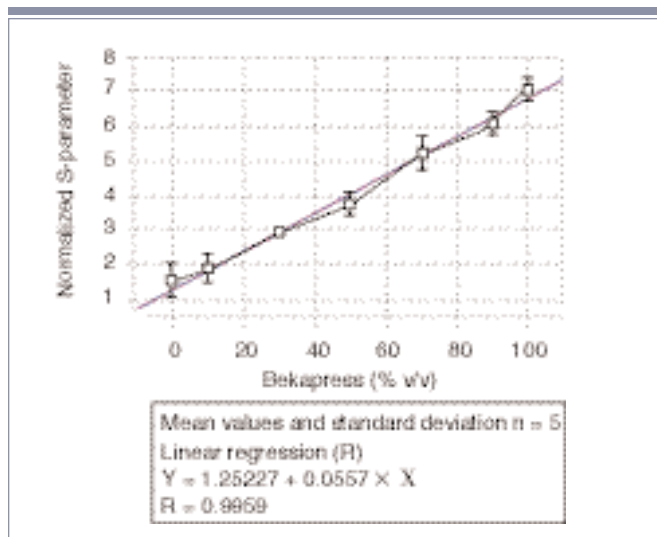


Figure 5: Normalized S-parameter versus Bekapress (v/v) for a binary mixture with MCC.

$$\text{Normalized S-parameter} = \frac{\text{S-parameter}}{\text{Compression force maximum}} \times 100 \quad [7]$$

Elastic behavior of binary mixtures

Three different binary mixtures were used to investigate the applicability of the Fraser-Suzuki function to such systems. The following excipient mixtures with different volume ratios (% v/v) were investigated:

- Avicel 102 with Bekapress D2
- Avicel 102 with potato starch
- Avicel 102 with PEG 6000.

Volume ratio as opposed to mass ratio was used because the volume occupation during compression is more important to the process than mass ratio (26,27).

For the evaluation, the normalized S-parameters were plotted against the volume ratios of the binary mixture, and all the mixtures were compressed to the same porosity. The first mixture (MCC and Bekapress) showed a linear relationship between the normalized S-parameters and volume ratio with a correlation coefficient of $R = 0.9959$. This can be observed as an improvement to the additive elastic behavior of this binary mixture (see Figure 5).

Increasing the Bekapress volume ratio caused an increase in the reversible deformation behavior of the mixture. This linearity could not be found during an investigation of the second binary system (potato starch with MCC). The curve showed a polynomial regression (second grade) with a correlation coefficient of $R = 0.997$ (see Figure 6). The linear regression resulted in a correlation coefficient of $R = 0.951$. The nonlinear behavior can be attributed to the interaction between potato starch and MCC during compression—MCC decreases the elastic behavior of the starch.

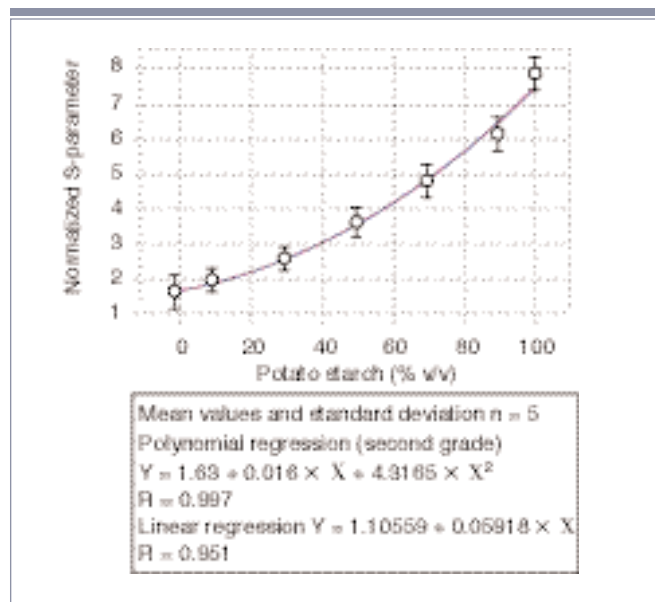


Figure 6: Normalized S-parameter versus various volume ratios of potato starch (% v/v) in the binary system of starch and MCC.

Compression of the third mixture (MCC and PEG 600) showed that the linear regression between the normalized S-parameter and the volume ratio was lower than previous mixtures. The correlation coefficient was $R = 0.91$ (see Figure 7).

This evidence demonstrates the distinctive interaction between both components. We believe the reasons for this distinctive interaction can be found in the thermomechanical properties of PEG 6000. PEG 6000 melts at a temperature of approximately 60 °C, which can be reached during the compression process so that a plasticizing effect of PEG on MCC is possible (28,29). The deformation behavior of the substances with higher volume ratios dominated the deformation behavior of the binary system, which can be seen during compression of MCC with PEG 600. A polynomial regression (third grade) with a correlation coefficient of $R = 0.9991$ could be made.

Table III: Evaluated function parameters with standard deviation (sd) by compression of starch to various porosities ($n = 5$).

A-parameter/sd	S-parameter/sd	tr-parameter/sd	Porosity (%)/sd
0.336 ± 0.010	0.271 ± 0.004	0.599 ± 0.004	30 ± 0.04
0.372 ± 0.012	0.263 ± 0.007	0.608 ± 0.007	25 ± 0.02
0.435 ± 0.004	0.265 ± 0.002	0.614 ± 0.003	20 ± 0.05
0.584 ± 0.006	0.258 ± 0.003	0.636 ± 0.005	15 ± 0.06
0.609 ± 0.009	0.248 ± 0.002	0.652 ± 0.003	10 ± 0.05

Table IV: The evaluated parameters with standard deviation (sd) of the Fraser-Suzuki function by compression of EC types to the same porosity of 15% ($n = 5$).

Ethylcellulose (EC)			
Type	A-parameter/sd	S-parameter/sd	tr-parameter/sd
EC 7cP	0.612 ± 0.004	0.195 ± 0.003	0.769 ± 0.005
EC 22cP	0.593 ± 0.004	0.201 ± 0.001	0.746 ± 0.003
EC 50cP	0.559 ± 0.003	0.215 ± 0.003	0.733 ± 0.007

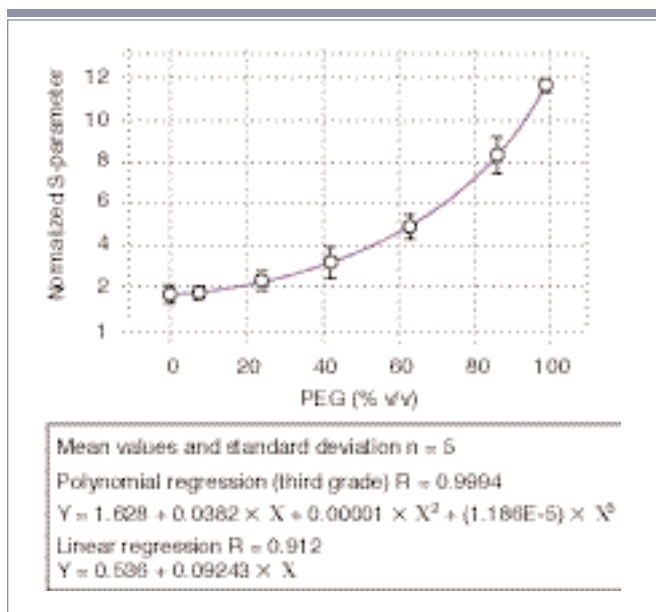


Figure 7: Normalized S-parameter versus various volume ratios of PEG 6000 (% v/v) in the binary system of PEG and MCC.

Conclusion

It can be postulated that the S-parameter of the modified Fraser-Suzuki function correlates with the \ln (Young's modulus) and allows a qualitative evaluation of the elastic deformation of pharmaceutical excipients. Furthermore, using the correlation coefficient of the linear regression between the normalized S-parameters and the volume ratio of one component in mixtures can provide a qualitative and quantitative evaluation of the interaction in binary mixtures.

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