PŮVODNÍ PRÁCE

Characterization of celluloses by means of viscoelastic parameters

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SUMMARY

Characterization of celluloses by means of viscoelastic parameters
In tablet formulation it is necessary to start from viscoelastic parameters of the excipients employed. Plasticity and elasticity of excipients are influenced by the type of bonds which are being formed in the course of the compaction process. The present paper evaluates the viscoelastic properties of selected fillers intended for direct compaction of tablets. The determinations included cellulose powder, microcrystalline celluloses Avicel PH 101, Avicel PH 102, Avicel PH 103, Avicel PH 200, Avicel PH 301, and Ceolus KG 802. Elasticity of the excipients was evaluated by means of Young's modulus of elasticity and differential elastic potential energy. Plasticity was evaluated by means of the stress relaxation test using the three-exponential equation following Maxwell's model. The method was supplemented with a novel original parameter, total plasticity P_T. The study examined the effect of particle size of fillers, density, moisture content, and molecular weight on elasticity and plasticity of celluloses. The results of the paper revealed that particle size of celluloses did not influence elasticity and plasticity of excipients. With increasing density of celluloses, elasticity was increased and at the same time plasticity was decreased. The above-mentioned viscoelastic parameters were influenced by the content of moisture in fillers. With increasing amount of moisture in fillers, elasticity was decreased and plasticity increased. With increasing molecular weight of cellulose, elasticity was decreased and plasticity increased.
Key words: Young's modulus of elasticity – differential elastic potential energy – three-exponential equation of plasticity – residual and total plasticity – celluloses

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SOUHRN

Charakterizace celulos pomocí viskoelastických parametrů
Při formulaci tablet je potřebné vycházet z viskoelastických parametrů použitých pomocných látek. Na jejich plasticitu a elasticitu má vliv typ vazeb formulujících se během lisovacího procesu. V této práci jsou hodnoceny viskoelastické vlastnosti vybraných plniv, určených pro přímé lisování tablet. Stanovení byly podrobeny prášková celulosa Vitacel A 300, mikrokrystalické celulosy Avicel PH 101, Avicel PH 102, Avicel PH 103, Avicel PH 200, Avicel PH 301 a Ceolus KG 802. Elasticita plniv byla hodnocena pomocí Youngova modulu pružnosti a diferenční elastické potenciální energie. Plasticita byla hodnocena pomocí relaxace napětí za použití trojexponenciální rovnice podle Maxwellova modelu. Tato metoda byla doplněna o nový originální parametr označený jako celková plasticita P_T. V práci byl sledován vliv velikosti částic plniv, hustoty, obsahu vlhkosti a molekulové hmotnosti na elasticitu a plasticitu celulos. Z výsledků práce vyplynulo, že velikost částic celulos neměla vliv na elasticitu a plasticitu plniv. Se vzrůstem hustoty celulos se elasticita zvyšovala a současně plasticita snižovala. Na uvedené viskoelastické parametry měl vliv

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obsah vlhkosti v plnivech. Se vzrůstem množství vlhkosti v plnivech se elasticita snižovala a plasticita zvyšovala. Se zvyšováním molekulové hmotnosti celulosy se elasticita snižovala a plasticita zvyšovala.
Klíčová slova: Youngův modul pružnosti – diferenční elastická potenciální energie – trojexponenciální rovnice plasticity – zbytková a celková plasticita – celulosy

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Introduction

Elasticity and plasticity are usually considered to be the principal viscoelastic properties. Elastic deformation can be defined as a reversible change in the shape or volume of material resulting from force, when after the action of force is completed, material returns to its original shape [1]. Elastic deformation is time-independent and fully restorable.

Plastic deformation can be defined as a permanent change in the shape of material resulting from applied tension [1]. The same author further points out that viscoelasticity reflect the time-dependent character of deformation.

In the evaluation of viscoelastic properties of fillers, four groups of methods are employed; the method based on the "force-route" record [2, 3], elastic recovery [4], creep test [5], and stress relaxation [6].

The present study evaluated plasticity of fillers by means of the stress relaxation test. If during compaction after reaching the maximal compaction force the upper punch is stopped and the volume of the tablet is left constant for a certain period of time, we can observe an exponential decrease in the strength in the tablet. Stress relaxation can thus be defined as a decrease in compaction force in time while keeping a constant volume of the material under compaction [7]. The extent of relaxation depends on the amount of energy stored in the tablet during compaction and also on bond formation [8].

For the evaluation of the decrease in strength during the test, one- to four-exponential equations are used [9]. The authors studied the behaviour of relaxation to 360 s and found that the graph of the decrease in strength in dependence on time corresponded to Maxwell's body 30 s after achieving the maximal strength. This model is composed of a spring and piston arranged in a series. The spring represents the elastic properties and the piston the plastic ones. The following equation corresponds to such a model:

$$F(t) = F_{MAX} \exp(t/T_0)$$

where F(t) is strength in time t and F_{MAX} the maximal strength in time 0, T_0 is the time constant.

Other authors [10] in their book present a simplified variant of the equation ($E_{1–3}$ – modulus of elasticity):

$$F(t) = E_1^{-t/T_1} + E_2^{-t/T_2} + E_3^{-t/T_3}$$

This study used the stress relaxation method to evaluate the viscoelastic characteristics of the fillers cellulose powder, and microcrystalline celluloses Avicel PH 101, Avicel PH 102, Avicel PH 103, Avicel PH 200, Avicel PH 301, and Ceolus 802.

EXPERIMENTAL PART

Raw materials used

The model pharmaceutical fillers for direct compression were the microcrystalline celluloses Avicel PH 101 (lot 6902C), Avicel PH 103 (lot Z726C), Avicel 301 (lot P926C), all manufactured by the firm FMC Corporation, Belgium; cellulose powder Vitacel A 300 (lot 0708050429), J. Rettenmaier, Germany, Ceolus KG-802 (lot K3B1), Asahi Kasei Chemicals Corporation, Japan. All materials comply with the European Pharmacopoeia and were used without any adjustments.

Preparation of tablets

Tablets of a diameter of 13 mm and weight of 500 mg were compacted in a compaction preparation (Adamus HT, Machine Factory Group, Szczecin, Poland) in a device for testing the strength of materials under tension and pressure T1-FRO 50 (Zwick GmbH, Ulm, Germany). Adjustment of the device: distance of jaws, 117 mm, rate of the cycle, 2 mm/s, pre-load, 2 N, compaction forces, 250 N, 500 N, 1000 N, 2000 N, 3000 N, 4000 N, 5000 N, 7500 N, 10000 N, 12500 N, and 15000 N. For the determination of Young's modulus of elasticity and elastic potential energy, tablets were compacted without a pause; for the determination of stress relaxation, tablets were compacted with a pause of 180 s. During the pause, the upper punch was stopped at the point where it reached the maximal strength, and the decrease in strength in the punch in dependence on time was recorded. In each compaction force, six tablets were evaluated.

When compaction was finished, the height of each tablet was measured (a digital micrometric screw Mitotuyo, Japan).

Calculation of Young's modulus of elasticity

Young's modulus of elasticity was calculated according to the equation:

$$CP = E_Y * \Delta l/l_0 ,$$

where CP is compaction pressure, E_Y Young's modulus of elasticity, and $\Delta l/l_0$ deformation expressed as the ratio of the change in the length of the body to the original height. The term Δl is the difference of heights of the tablets 5 s after completion of compaction and the height at the maximal pressure, l_0 is the height of the tablet at the maximal pressure. In the graphic representation of the dependence of CP on l/l_0, the gradient of the developed line is the Young's modulus of elasticity which is searched for.

Calculation of elastic potential energy

The following equation served to calculate elastic potential energy, which causes the increase in height of the tablet after the completion of compaction [11]:

$$E = \left[\left(\frac{LT}{\frac{\Delta l}{l_0}} \right) * A * \Delta l^2 \right] / 2\, l_0 \ [J]$$

where A is the area of the tablet (m^2), other terms are explained above.

The differences in elastic potential energy of the tablets compacted without a pause and those with a pause yielded differential elastic potential energy (J).

Calculation of stress relaxation parameters

To calculate the parameters of the decrease in strength in the tablet at 180 s with a pause, the following three-exponential equation is employed:

$$CP = E_1 e^{-t/T_1} + E_2 e^{-t/T_2} + E_3 e^{-t/T_3} \ [MPa]$$

Parameters of the above-mentioned equation were calculated using the programme OriginPro 7.5 by means of the function ExpDec3. The parameter CP (MPa) is the compaction pressure at a given moment in time t (s), $E_{1\text{-}3}$ (N) is the amount of strength which was decreased in the given process, $T_{1\text{-}3}$ is the relaxation constant which states the rate and the steep gradient of the process. The residual plasticity P_R (MPas) is calculated from the following equation [10]:

$$P_{Ri} = E_i * T_i \quad [MPas]$$

for each compaction pressure. The total plasticity P_T (MPas) is then equal to the area under the curve of the graph of the dependence of P_R/CP on CP.

RESULTS AND DISCUSSION

The stress relaxation test was employed to evaluate plasticity. The results obtained in this test expressing the decrease in compaction pressure in dependence on time were evaluated by means of a three-exponential equation. This equation corresponds to three Maxwell's models arranged in parallel[10]. The springs $E_{1–3}$ represent the elastic modulus, the pistons $P_{R1–3}$, the plastic modulus. After compaction of the material by a certain pressure, a certain value of the spring E and the zero value of P_R are achieved.

The given relation divides the whole process of decrease in compaction pressure in dependence on time into three processes. According to the present authors' idea, in the first process a high decrease in the modulus E_1 is due to the extension of the spring in order to achieve greater mutual approximation of the surfaces of the particles. The given approximation does not result in the development of new bonds yet. That is why the increase in the value of the modulus of the residual plasticity P_{R1} is minimal. In the second process it can be assumed that by the action of smaller released elastic energy further approximation of the surfaces of the particles occurs and conditions are produced for the development of bonds. In the third process, the elastic modulus E_3 possesses approximately the same value as the parameter E_2 and at the same time a high value of the modulus of the residual plasticity P_{R3}. This process is called the plastic process, in which deformation is not restorable and the process is time-dependent [12–14]. In the third process, only a small amount of elastic energy suffices for further approximation of the surfaces of the particles and development of bonds.

Viscoelastic properties were studied in cellulose powder and in microcrystalline celluloses, which possess substantially smaller molecular weights than cellulose powder. The microcrystalline celluloses employed differ in the sizes of particles, densities, and moisture content.

The obtained results are shown in Tables 1 and 2 and in Figures 1–6. In the graphs there are obviously great standard deviations in some parameters. They are caused by close affinities of the excipients tested and further by the use of original methodologies producing greater variability of results.

The first marker under evaluation was molecular weight of the celluloses. Cellulose powder possesses the molecular weight of about 243000, microcrystalline celluloses only about 36000 [15]. For the evaluation of viscoelastic parameters, a comparison was made of the properties of cellulose powder and the microcrystalline cellulose Avicel PH 102. Young's modulus of elasticity in cellulose powder in comparison with Avicel PH102 was higher by 10 MPa and differential elastic potential energy was higher by 0.51 J. The higher values in both cases mean lower elasticity. On the other hand, the values of plasticity in all three processes were higher in cellulose powder. The parameter P_{T1} was higher by 0.73 MPas, the parameter P_{T2} higher by 8.33 MPas, and the parameter P_{T3} higher by 146.32 MPas. Cellulose powder in contrast to Avicel PH 102 thus showed lower elastic properties and at the same time higher plasticity. These regularities are caused by the type and number of bonds which are being formed during compaction process. Cellulose powder, in contrast to Avicel PH 102, possesses a low crystalline share and at

Table 1. Values of elastic parameters of celluloses. E_Y Young's modulus of elasticity and E_{EP} differential elastic potential energy (X arithmetic mean, s standard deviation)

Excipients	E_Y (MPa) X	s	E_{EP}(J) X	s
Avicel 101	523.8134	15.7363	1.98656	0.0896
Avicel 102	519.5693	6.8552	1.71617	0.0851
Avicel 103	496.27606	17.89169	1.78479	0.0741
Avicel 200	521.82148	12.79383	1.79371	0.0962
Avicel 301	506.25159	17.12044	1.50009	0.0763
Ceolus KG802	529.06392	21.67744	1.8646	0.0652
Cellulose	529.06392	20.9247	2.22892	0.0813

Table 2. Value of total plasticity P_T of celluloses (X arithmetic mean, s standard deviation)

Excipients	P_{T1}(MPas) X	s	P_{T2}(MPas) X	s	P_{T3}(MPas) X	s
Avicel 101	3.31519	0.12466	25.41819	1.26466	409.35295	7.54664
Avicel 102	3.2493	0.13476	25.01409	1.33648	411.64793	5.45646
Avicel 103	3.54523	0.14567	26.61327	1.02346	389.70323	10.15465
Avicel 200	3.36512	0.11546	25.24299	1.64212	408.10231	6.32546
Avicel 301	3.42389	0.15644	24.66458	1.23446	400.55752	6.46755
Ceolus KG 802	3.44447	0.12546	26.24812	1.21346	409.64852	8.14564
Cellulose	3.98325	0.15888	33.34236	2.01546	557.967	9.1853

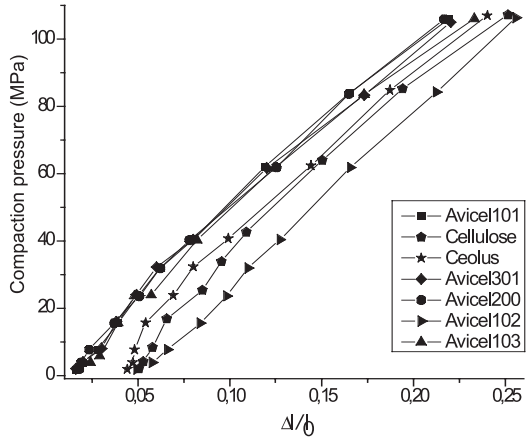

Fig. 1. Relationship between compaction pressure and $\Delta l/l_0$

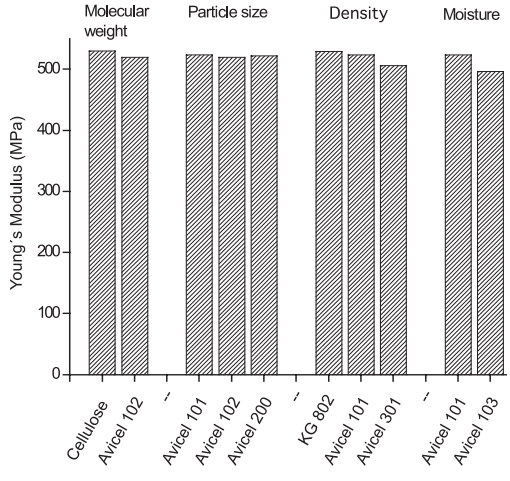

Fig. 2. Effect of factors under study on Young's modulus of elasticity in celluloses

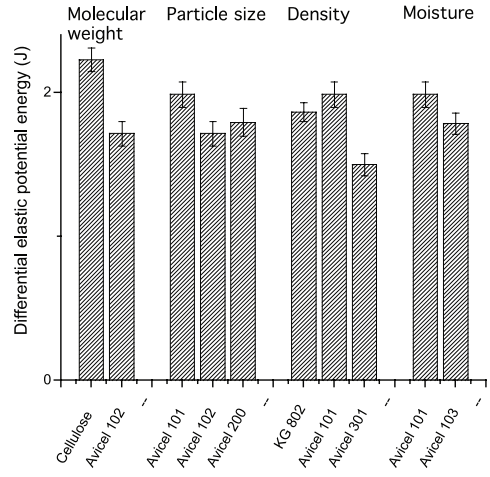

Fig. 3. Effect of factors under study on E differential elastic potential energy in celluloses

the same time a larger amorphous share, which on compaction readily forms hydrogen bonds. Also in cellulose powder, in contrast to Avicel PH 102, the principle of mechanical interlocking plays its role [16].

Another marker under evaluation is particle size. In this part of the study, Avicel PH 101 with a particle size of 50 μm, Avicel PH 102 with a particle size of 100 μm, and Avicel PH 200 with a particle size of 180 μm were compared. The values of Young's modulus of elasticity ranged from 522 to 524 MPa, the values of differential elastic potential energy from 1.72 to 1.99 J, and the values of plasticity P_{T1} from 3.25 to 3.36 MPas, P_{T2} from 25.01 to 25.41 MPas, and P_{T3} from 408.10 to 411.65 MPas. The results cannot clearly demonstrate the effect of particle size on viscoelastic properties of microcrystalline celluloses. It is due to the method of production,

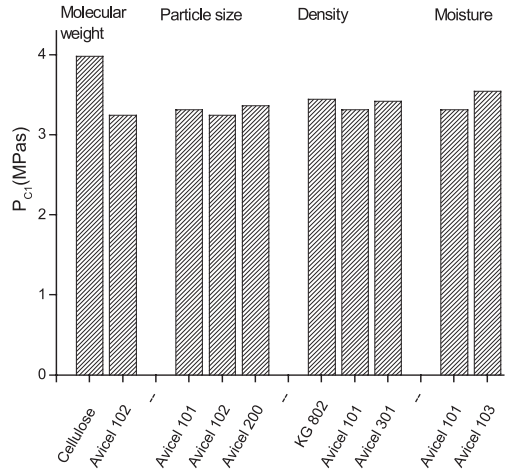

Fig. 4. Effect of factors under study on total plasticity P_{T1} in celluloses

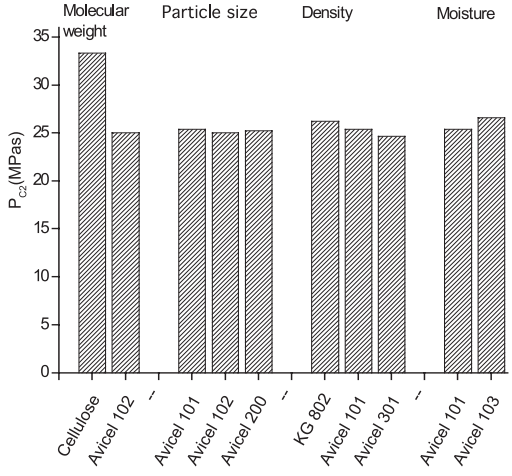

Fig. 5. Effect of factors under study on total plasticity P_{T2} in celluloses

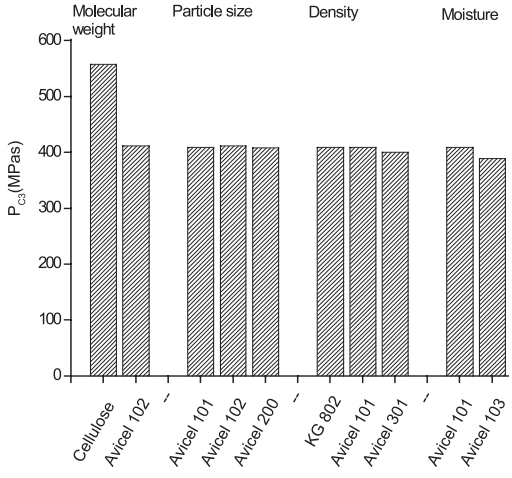

Fig. 6. Effect of factors under study on total plasticity P_{T3} in celluloses

when the primary needle-shaped objects of the size of about 20 μm granulate into the objects of varying particle sizes. The microcrystalline celluloses under study of varying sizes therefore possess the same compaction properties.

Another important factor is the density of microcrystalline celluloses. The comparison included Ceolus KG 802 with a density of 0.2 g/cm^2, Avicel PH 101 with a density of 0.3 g/cm^2, and Avicel PH 301 with a density of 0.4 g/cm^2 [15]. Young's modulus decreased with increasing density from 529 to 506 MPa and differential elastic potential energy decreased from 1.99 to 1.50 J. With a decrease in the values of the above-mentioned parameters, elasticity of microcrystalline celluloses was increased. The parameter of plasticity P_{T1} ranged from 0.44 to 3.32 MPas. With low values it is not possible to assume a significant influence of the factor under studies. The parameter P_{T2} decreased from the value of 26.25 MPas to the value of 24.66 MPas and the parameter P_{T3} also decreased from the value of 406.65 MPas to the value of 400.56 MPas. Plasticity of microcrystalline celluloses generally decreased with increasing density.

The final parameter under evaluation was the declared moisture content of microcrystalline celluloses, comparing Avicel PH101 with a moisture content of 5% and Avicel PH 103 with a moisture content of 3%.

Young's modulus of elasticity in Avicel PH 101 was 524 MPa and in Avicel PH 103 496 MPa. Differential elastic potential energy in Avicel PH 101 was 1.99 J and in Avicel PH 103, 1.79 J. With a decreasing moisture content in the particles of microcrystalline cellulose, elasticity was increased. When comparing plasticities, with an increasing moisture content the parameter P_{T1} ranged insignificantly from 3.32 MPas to 3.55 MPas, the parameter P_{T2} ranged insignificantly from 25.41 MPas to 26.25 MPas. On the other hand, the principal parameter necessary for the formation of bonds P_{T3} decreased with decreasing moisture from 409.35 MPas to 389.70 MPas. A decreasing moisture content in microcrystalline celluloses decreases plasticity by decreasing the number of hydrogen bonds, which are being formed during compaction process.

An important characteristic of fillers is their plasticity. The present paper has demonstrated that cellulose powder possesses higher plasticity than other microcrystalline celluloses. Furthermore, it has been demonstrated that plasticity is not influenced by particle size of microcrystalline celluloses. Plasticity is further increased with decreasing density of microcrystalline celluloses and increasing moisture in the particles of microcrystalline celluloses.

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NOVÉ KNIHY

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Jedná se o třetí příručku z řady zpráv věnovaných důležité problematice – správné výrobní praxi (SVP či GMP), kterou řídí firma Concept z Heidelbergu. Pod pojmem rizik rozumíme nebezpečí nezdaru, ztrát i ekonomických, a je to hlavní motivační prvek ovlivňující rozhodnutí podnikatelů vyplývající nutnost správné optimální volby. Jedním z principů snižování rizik je možné rozdělení velkého rizika na řadu menších rizik.

Celková tematika se v příručce dělí do čtyř základních kapitol: 1. Požadavky na řízení rizik z hlediska současných předpisů platných v německých farmaceutických továrnách; 2. Přehledy hlavních rizik při používání strojů a dalších zařízení ve farmaceutických provozech. 3. Příklady řešení nejdůležitějších rizik jak ve farmaceutické výrobě, tak i v kontrole. Poměrně obsáhlá část se zabývá právními aspekty vzniku a možnostmi odkrývání, jakož i řešení různých rizik, a to při výrobě tablet i při výrobě dražé. Důležitou fází je také riziko při klasifikaci analytických přístrojů a mikrobiologických metod, jakož i základy validace spolehlivosti všech kontrolních systémů. Zvýšená pozornost je zaměřena na rizika ve výrobě kusových léků, a to tablet i dražé. Pro větší přehlednost jsou jednotlivé pracovní operace uspořádány do přehledných tabulek s uvedením možných rizik a jejich odstranění, a to od použitých surovin, výrobních zařízení až po balení. 4. Uplatnění moderní výpočetní techniky při řízení a kontrole (řešení) výskytu nejrůznějších rizik. Ke zlepšení textu se v něm často využívá různých zkratek, např. HACCP (to značí Hazard Analysis Critical Control Points) = tato metoda vyvinutá pro potřeby potravinářského průmyslu v Evropě a lze ji také využívat ve farmaceutickém průmyslu. Odkazy na citace z farmaceutických publikací i ekonomických prací jsou součástí každé kapitoly. Závěrem je připojen seznam hlavních spoluautorů (10) uspořádaný abecedně s adresami i pracovišti (jeden je z Anglie a Rakouska, dva jsou ze švýcarských farmaceutických podniků a šest pak z Německa).

Příručka je svým řešením velmi zajímavá a najde svoje praktické využití při řešení různých druhů rizik při farmaceutické výrobě.

J. Malý