

# Characterization of microcrystalline celluloses by means of the parameters of a three-exponential compression equation

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## SUMMARY

### Characterization of microcrystalline celluloses by means of the parameters of a three-exponential compression equation

The study compares microcrystalline celluloses by means of the parameters of the three-exponential equation  $V/V_0 = A_1 \cdot \exp(-P/t_1) + A_2 \cdot \exp(-P/t_2) + A_3 \cdot \exp(-P/t_3) + y_0^{-1}$ . The process of compression, according to this equation, takes place in three stages: in the stage of reduction of interparticular pores, reduction of intraparticular pores, and in the stage of reduction of the solid substance without pores. The classic theory of compression is based on the fact that the individual processes take place within the ranges of concrete compression pressures. According to the new equations, the processes under evaluation take place concurrently within the whole range of compression pressures employed. The paper studied four microcrystalline celluloses, Avicels PH 102, PH 103, PH 105, and PH 301. These excipients differ in sizes and shapes of particles, density, and content of humidity. The evaluations included the sizes of reductions  $A_R$ , sizes of energies  $E_A$ , and "half-pressures"  $P_H$ . The results of the study show that with diminishing particles of microcrystalline celluloses energies  $E_A$  are decreased and "half-pressures" are simultaneously increased. Best compressibility was found in Avicel PH 102 with the value of the "half-pressures" of 119.954 MPa and the worst in Avicel PH 301 with the value of the "half-pressures" of 151.449 MPa.

**Key words:** three-exponential equations of compression – microcrystalline celluloses – theory of compression of tablets

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## SOUHRN

### Charakterizace mikrokrytalických celulos parametry trojexponenciální rovnice lisování

V práci jsou mikrokrytalické celulosy porovnány pomocí parametrů trojexponenciální rovnice  $V/V_0 = A_1 \cdot \exp(-P/t_1) + A_2 \cdot \exp(-P/t_2) + A_3 \cdot \exp(-P/t_3) + y_0^{-1}$ . Proces lisování pomocí této rovnice probíhá ve třech fázích, ve fázi redukce interpartikulárních pórů, redukce intrapartikulárních pórů a ve fázi redukce tuhé látky bez pórů. Klasická teorie lisování vychází ze skutečnosti, že jednotlivé procesy probíhají v rozmezí konkrétních lisovacích tlaků. Podle nových rovnic hodnocené procesy probíhají souběžně v celém použitém rozsahu lisovacích tlaků. V práci byly studovány čtyři mikrokrytalické celulosy, Avicely PH 102, PH 103, PH 105 a PH 301. Tyto pomocné látky se liší velikostí a tvarem částic, hustotou a obsahem vlhkosti. Byly hodnoceny velikosti redukce  $A_R$ , velikosti energií  $E_A$  a „půltlaky“  $P_H$ . Z výsledků práce vyplynulo, že se zmenšováním částic mikrokrytalických celulos se energie  $E_A$  snižují, současně se „půltlaky“ zvyšují. Nejlepší lisovatelnost má Avicel PH 102 s hodnotou „půltlaku“ 119,954 MPa a nejhorší lisovatelnost Avicel PH 301 s hodnotou „půltlaku“ 151,449 MPa.

**Klíčová slova:** trojexponenciální rovnice lisování – mikrokrytalické celulosy – teorie lisování tablet

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## Introduction

The compression process is characterized by the compression equation. It expresses the effect of compression pressure on the changes in the height, volume, or density of the tablet. At present the research of tablets uses three models of compression equations. The first and oldest model is the expression of the compression process by a straight-line equation. This model is represented by the equation according to Walker <sup>2)</sup> and Balshin <sup>3)</sup>. The second model expresses the compression process by the hyperbolic equation, an example being the equation according to Kawakita and Lüdde <sup>4)</sup>. The third model is the expression of the compression process by means of a two-exponential equation. This method was employed by Cooper and Eaton <sup>5)</sup>. This equation was created for the compression of ceramic materials. It has been found that the above-mentioned equation describes the compression process of crystalline pharmaceutical excipients, but it is not suitable for polymeric excipients. The three-exponential equation is more suitable for these substances:

$$\frac{V}{V_0} = A_1 e^{-\frac{1}{t_1} P} + A_2 e^{-\frac{1}{t_2} P} + A_3 e^{-\frac{1}{t_3} P} + y_0$$

$V_0$  is the initial volume of the tableting material which is being compressed,  $V$ , the volume of the tableting material at a given compression pressure. The parameter  $y_0$  represents the volume of the compact  $V_\infty$  at the endless compression pressure.  $P$  are the compression pressures. Parameter  $A_1$  represents the reduction of interparticular pores, parameter  $A_2$  the reduction of intraparticular pores, and parameter  $A_3$  the reduction of the solid substance without pores. Parameters  $1/t_{1-3}$  are the velocity constants of the appropriate reductions of volumes, out of which other parameters  $P_{H1-3}$  are calculated. These parameters express the compression pressures, up to which one half of the reduction of interparticular pores, intraparticular pores, or the reduction of the solid substance without pores take place. The new parameters  $E_{1-3}$  express the energy consumed to materialize the given reductions of the volume. The parameters  $E_{A1-3}$  express the energy related to a unit of parameter  $A$ , i.e. a unit of the reduction of volumes in individual processes.

The study included the microcrystalline celluloses Avicel PH 102, PH 103, PH 105 and PH 301.

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## EXPERIMENTAL PART

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### Raw materials employed

The model dry binders for direct compression were the microcrystalline celluloses Avicel PH102, PH 103, PH 105, PH 301 manufactured by the firm FMC Corporation, Belgium. All materials were Ph. Eur. grade and used as purchased without preconditioning.

## Preparation of tablets

Tablets of the diameter of 13 mm and weight of 500 mg were compressed in a compression preparation (Adamus HT, Machine Factory Group, Szczecin, Poland) in an apparatus for testing tensile and compression strengths T1-FRO 50 (Zwick GmbH, Ulm, Germany). Tablets were compressed using the following adjustment of the apparatus: distance of the punches 115 mm, standard strength 42000 N, unloading of the cycle 10 mm, velocity of the cycle 2 mm/s, pre-loading 2N, and pre-loading velocity 2 mm/s at the following compression forces: 50N, 100N, 150N, 200N, 250N, 300N, 350N, 400N, 450N, 500N, 750N, 1000N, 1500N, 2000N, 2500N, 3000N, 3500N, 4000N, 4500N, 5000N, 5500N, 6000N, 6500N, 7000N, 7500N, 8000N, 8500N, 9000N, 9500N, 10000N, 11000N, 12000N, 13000N, 14000N, 15000N, 16000N, 17000N, 18000N, 19000N, 20000N, 22000N, 24000N, 26000N, 28000N, 30000N, 32000N, 34000N, 36000N, 38000N, 40000N. In each of the compression forces 20 tablets were evaluated.

### Evaluation of the parameter of the compression process

The following three-exponential equation of compression was employed to calculate the parameters of the compression process:

$$\frac{V}{V_0} = A_1 e^{-\frac{1}{t_1} P} + A_2 e^{-\frac{1}{t_2} P} + A_3 e^{-\frac{1}{t_3} P} + y_0$$

The parameters of the above-mentioned equations were calculated by means of the programme OriginPro 7.5 by the function ExpDec3. The sum of parameters  $A_{1-3}$  and  $y_0$  represents the total volume of the compressed material at zero compression pressure. Parameter  $y_0$  represents the volume of the solid substance at endlessly large compression pressure. For a better comparison of the individual excipients, the sum of the reductions  $A_1, A_2$  and  $A_3$  was converted to the value of 1.0, thus obtaining parameters  $A_{R1}, A_{R2}$  and  $A_{R3}$ . Volume changes in all tested substances thus ranged between 0 and 1. After this modification, the following equation was obtained:

$$\frac{V}{V_0} = A_{R1} e^{-\frac{1}{t_1} P} + A_{R2} e^{-\frac{1}{t_2} P} + A_{R3} e^{-\frac{1}{t_3} P}$$

Values  $t_1, t_2, t_3$  represent changes in compression pressure which cause a change in the volume  $V/V_0$  to a certain value. These parameters were employed to calculate the "half-pressures" and the energy of compression.

Values  $t_1, t_2, t_3$  served to calculate parameters  $P_{H1}, P_{H2}, P_{H3}$ . These new parameters, "half-pressures", express the compression pressures at which reductions of interparticular pores, intraparticular pores, or reduction of a solid substance without pores to one half take place.

New parameters were calculated according to the following equations:

$$V(t) = Ae^{\frac{-t}{t_i}}$$

$$Ae^{\frac{-t + \Delta t}{t_i}} = \frac{Ae^{\frac{-t}{t_i}}}{2}$$

$$\Delta t = t \ln 2$$

The following relations were employed to calculate the percentages of the energies of individual processes from parameters  $t_1$ ,  $t_2$ ,  $t_3$ :

$$dV = V'(P)dP$$

$$dE = P \cdot V'(P)dP$$

This results in the conclusion that there is a dependence of the travel on force, but because the resultant energy is expressed in percents and calculated from relations (see the relation shown below), the percentual representation of energy for each process is identical also as far as the dependence of the ratio volume  $V/V_0$  on compression pressure  $P$  is concerned.

The calculation of the percentage of energy for each process uses the equation:

$$E_i = \frac{A_i t_i}{\sum A_i t_i} \%$$

Energies  $E_{A1-3}$  related to reductions of volumes were calculated according to the equation:

$$E_{A_i} = \left( \frac{E_i}{A_i} \right) [\%]$$

## RESULTS AND DISCUSSION

Due to their good compressibility, microcrystalline celluloses are widely used excipients in the capacity of a filler for direct compression or a binder for most granulation <sup>6)</sup>.

Cellulose fibres are composed of a large number of hollow microfibrils. Two segments are recognized in these microfibrils. There is a paracrystalline region, which is amorphous mass of cellulose chains, and a crystalline region, which is composed of solid bundles of cellulose chains in a solid linear arrangement. In their manufacture, as a result of acid hydrolysis, the amorphous region is partly removed to the detriment of the crystalline region <sup>7)</sup>.

The binding properties are based on the hydrogen bridges between hydroxyl groups of the material. By means of compression pressure, the particles get into a very close contact and thanks to it these bonds develop very readily and on a large area. This is the reason for very good compression properties of microcrystalline cellulose and its good strength. Compression properties of microcrystalline cellulose are also influenced by humidity. The largest amount of water molecules is contained in the porous structure of microcrystalline cellulose and a certain share of moisture plays an important role in the formation of hydrogen bonds in these materials <sup>8)</sup>.

Four microcrystalline celluloses were evaluated in the study. The obtained results are presented in Tables 1–3 and Figs. 1–5. The principal microcrystalline cellulose for the evaluation was Avicel PH 102. It possesses an

Tab. 1. Comparison of densities in the excipients under study (abbreviations of densities are explained in the paper)

Excipients	$D_{MAX}$ (g/cm <sup>3</sup> )	$D_{40kN}$ (g/cm <sup>3</sup> )
Avicel PH 102	4.7562	2.6987
Avicel PH 103	4.9305	2.8562
Avicel PH 105	5.4603	2.8406
Avicel PH 301	6.5079	2.8805

Tab. 2. Parameters  $A_{R1-3}$  and  $E_{1-3}$  in the excipients under study (abbreviations of parameters of compression are explained in the paper)

Excipients	$A_{R1}$	$A_{R2}$	$A_{R3}$	$E_1$ (%)	$E_2$ (%)	$E_3$ (%)
Avicel PH 102	0.19433	0.44423	0.36143	0.62112	9.2889	90.08997
Avicel PH 103	0.19132	0.428	0.38068	0.54727	8.79587	90.65686
Avicel PH 105	0.18911	0.34593	0.46496	0.33113	6.32171	93.34716
Avicel PH 301	0.16322	0.36742	0.46936	0.35827	7.11988	92.52185

Tab. 3. Parameters  $E_{A1-3}$  and  $P_{H1-3}$  in the excipients under study (abbreviations of parameters of compression are explained in the paper)

Excipients	$E_{A1}$ (%)	$E_{A2}$ (%)	$E_{A3}$ (%)	$P_{H1}$ (MPa)	$P_{H2}$ (MPa)	$P_{H3}$ (MPa)
Avicel PH 102	0.03197	0.20910	2.49266	1.53875	10.06267	119.95434
Avicel PH 103	0.02860	0.20550	2.38169	1.53051	10.99600	127.43669
Avicel PH 105	0.01751	0.18272	2.00784	1.19852	12.50938	137.48639
Avicel PH 301	0.02195	0.19378	1.97128	1.68669	14.88778	151.44941

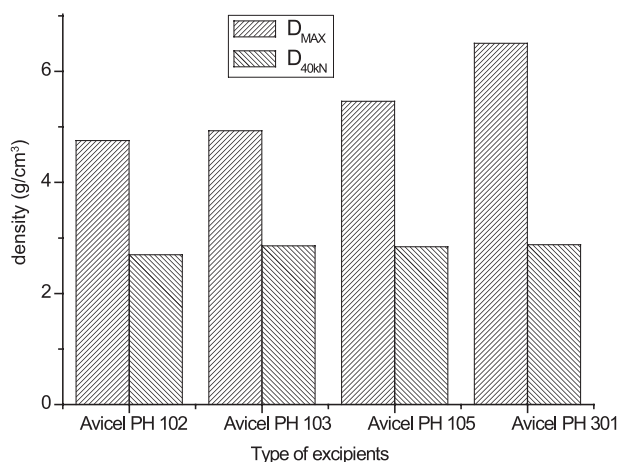


Fig. 1. Densities in the excipients under study (abbreviations of densities are explained in the paper)

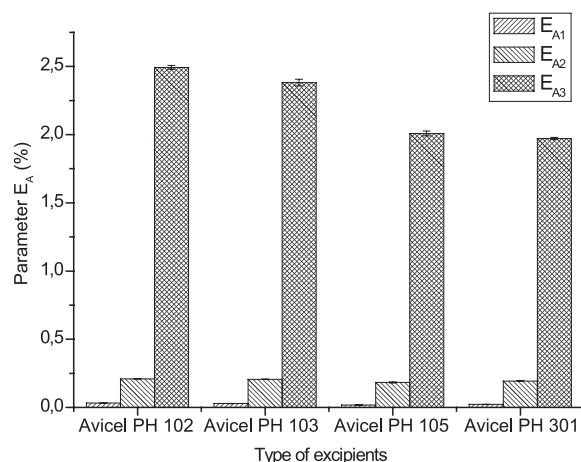


Fig. 4. Parameters  $E_{A1-3}$  in the excipients under study (all columns displayed means of  $n = 20$  with 1s error bars)

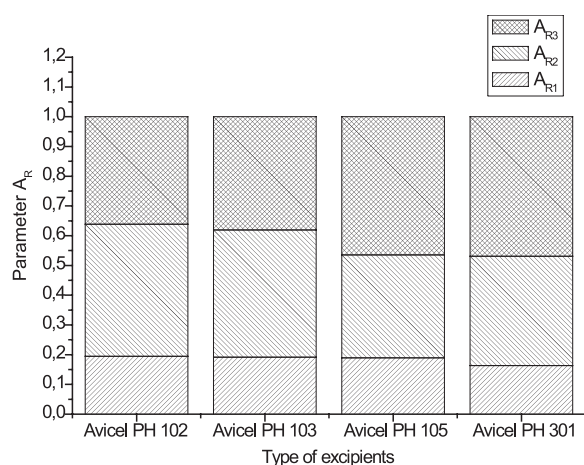


Fig. 2. Parameters  $A_{R1-3}$  in the excipients under study

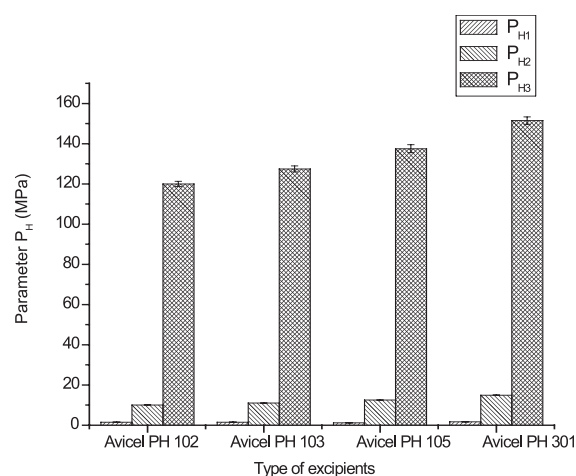


Fig. 5. Parameters  $P_{H1-3}$  in the excipients under study (all columns displayed means of  $n = 20$  with 1s error bars)

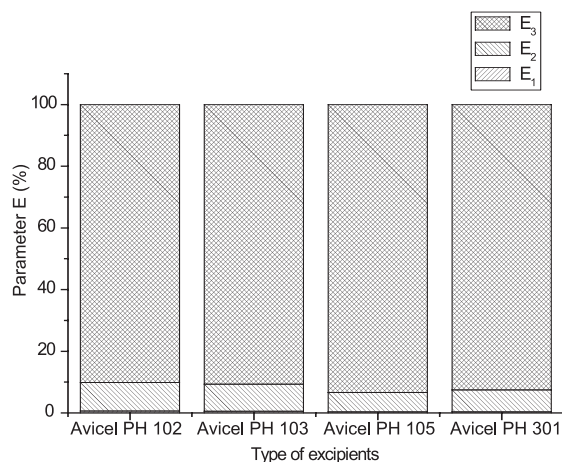


Fig. 3. Parameters  $E_{1-3}$  in the excipients under study (all columns displayed means of  $n = 20$  with 1s error bars)

average particle size of 100  $\mu\text{m}$ , humidity 5%, and density  $D_{MAX}$  4.756 g/cm<sup>3</sup>. This substance possesses the parameters  $A_{R1}$  0.194,  $A_{R2}$  0.444 and  $A_{R3}$  0.361 and  $E_{A1}$  0.032%,  $E_{A2}$  0.209%,  $E_{A3}$  2.492% and the “half-pressures”  $P_{H1}$  1.539 MPa,  $P_{H2}$  10.063 MPa and  $P_{H3}$  119.954 MPa.

Avicels PH 103 and PH 105 in comparison with Avicel PH 102 possess an approximately identical density  $D_{MAX}$ , but they differ in the average particle size. Avicel PH 103 has the size of 50  $\mu\text{m}$  and Avicel PH 105 20  $\mu\text{m}$ . Reductions of interparticular pores between three Avicels under comparison are approximately identical. However, the evaluation of other two parameters is different. With increasing particle size the reduction of intraparticular particles is increased and at the same time the reduction of the solid substance without pores is decreased. The parameters of reductions of volumes are related directly to particle size and thus the pertinent relations after poring of the excipient into the matrix. With decreasing particle size, energies  $E_A$  are decreased in all three stages of the compression process. It seems that the bonds between surface chains of cellulose consume less energy than those between the chains within the particles. The final criterion of evaluation is “half-pressures”. In the stage of reduction of interparticular pores, “half-pressures” in all three microcrystalline celluloses are approximately identical in the range from 1.199 to 1.538 MPa. But in two subsequent stages the “half-pressures” are increased with

the decreasing particle size, in the stage of reduction of intraparticle pores in the range from 10.063 to 12.509 MPa and in the stage of reduction of the solid substance without pores in the range from 119.954 to 137.437 MPa. It means that with the diminishment of the particles of microcrystalline celluloses energies  $E_A$  are decreased with a concurrent increase in the “half-pressure” values.

Another microcrystalline cellulose under evaluation is Avicel PH 301. It differs from Avicel PH 102 in a substantially higher density  $D_{MAX}$  at the level of 6.507 g/cm<sup>3</sup>. Its particle size is 50 µm and humidity content, 5%. In contrast to Avicel PH 102, it has lower values of reductions of both interparticle and intraparticle pores, which may be caused by its particle size. On the other hand, the reduction of the solid substance without pores is higher, caused probably also by a higher density. Energies  $E_A$  in Avicel PH 301, in contrast to Avicel PH 102, are in all three stages of compression process lower and “half-pressures” higher.

An important criterion of evaluation is the values of “half-pressures”. Lower values in the stage of reduction of the solid substance without pores mean better compressibility. From the given aspect, the best compressibility is found in Avicel PH 102 with the “half-

pressure” value of 119.954 MPa and the worst compressibility in Avicel PH 301 with the “half-pressure” value of 151.449 MPa.

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