Physicochemical properties of granulating liquids and their influence on microcrystalline cellulose pellets obtained by extrusion-spheronisation technology

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Abstract

The use of ethanol or ethanol/water mixtures as granulation liquids in the extrusion-spheronisation process results in the formation of pellets with significantly different mechanical and structural properties from those prepared using water alone. The product of surface tension (γ_L), relative permittivity (ε_R) of the granulation liquid and the cosine of contact angle (Θ) of granulation liquid on pellets solid has been introduced in order to explain the mechanism of this phenomenon. A correlation is shown between the factor $\gamma_L \times \cos(\Theta) \times \varepsilon_R$ and the properties of the pellets produced. We have introduced the $\gamma_L \times \cos(\Theta) \times \varepsilon_R$ which can be considered to represent the driving and counteracting forces of pellet contraction during drying. The contact angles and surface tensions were evaluated using the Wilhelmy plate method. Pellets were produced by extrusion-spheronisation technique using water, ethanol and ethanol/water mixtures as granulation liquids. Subsequent characterization of the pellets showed that their tensile strength and disintegration times increase with increase in the proposed factor $\gamma_L \times \cos(\Theta) \times \varepsilon_R$, while friability, average pore diameter and porosity decreases. The observed correlations show, that the granulation liquid influences the mechanical and structural properties of the pellets through the contraction driving and contraction counteracting forces during drying.
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1. Introduction

Use of non-water granulation liquids is imperative, when incorporating certain active substances into

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Nomenclature

A_{BET}	five-point BET surface area
A_H	Hamaker constant
E	van der Waals energy of interaction
$E_\%$	porosity of a pellet
F	failure load
h	distance between two surfaces
m	Weibull-modulus
m_a	mass of pellet after the mechanical stress
m_b	mass of pellet before mechanical stress
P/P_0	relative pressure
P_0	saturation pressure
P_R	maximum capillary pressure
R	radius of the pellet
r_H	hydraulic radius
T	temperature
V	single point adsorption total pore volume
x_0	characteristic pellet strength
x_E	mole fraction of ethanol
x_W	mole fraction of water
x_u	plasticity term
γ_L	surface tension of a liquid
γ_L^d	dispersive component of the surface free energy for a liquid
γ_L^p	polar component of the surface free energy for a liquid
γ_S^d	dispersive component of the surface free energy for a solid
γ_S^p	polar component of the surface free energy for a solid
ε^E	excess permittivity
ε_{ideal}	ideal relative permittivity of a mixture
ε_{mix}	relative permittivity of the mixture
ε_R	relative permittivity
ε_{rE}	relative permittivity of ethanol
ε_{rW}	relative permittivity of water
Θ	contact angle of liquid on a solid surface
ρ_a	apparent particle density
ρ_e	effective particle density
$\sigma_f(s)$	surface tensile stress

pellets by means of wet granulation in order to improve their chemical and/or physical stability. Another application of use of water in mixture with other pharmaceutically accepted liquid as granulation liquid is in controlling the mechanical properties of the pellets produced to improve the tabletting behaviour of pellets (Johansson et al., 1995).

The objective of this study was to elucidate the relation between the mechanical and structural properties of pellets produced by extrusion-spheronisation and the physicochemical properties of used granulation liquid. It has been shown that use of ethanol, ethanol/water mixtures, 2-propanol and 2-propanol/water mixtures result in the formation of pellets that have significantly different mechanical and structural properties from those obtained when pure water is used (Millili and Schwartz, 1990; Schröder and Kleinebudde, 1995). In these studies, the properties of the pellets were given as a function of composition of the granulation liquids, i.e., mole or mass fraction of ethanol or 2-propanol. In our study, we have correlated tensile strength ($\sigma_f(s)$), disintegration time, friability and average pore diameter of pellets with the product of surface tension (γ_L), relative permittivity (ε_R) of the granulation liquid and cosine of the contact angle (Θ) of the granulation liquid with the pellet solid. In addition to explaining how a granulation liquid influences pellet properties, this approach offers the possibility of universality, as the system is described solely by the physicochemical properties of the granulation liquid.

To ease the interpretation of the results obtained, a single component pellet system has been studied. Microcrystalline cellulose (MCC) has been chosen, as it is a requisite excipient in extrusion-spheronisation process; water, ethanol and ethanol/water mixtures have been used in wet granulation. Because MCC is not soluble in water or ethanol and only swells in water, it is assumed that van der Waals interactions are the main interparticle bonding mechanism and, therefore, define the mechanical properties of the dry agglomerate, i.e., pellet. This is further confirmed by the finding that differences in the mechanical strength of dried MCC pellets are not due to significant changes in the degree of hydrogen bonding when water or ethanol/water mixture are used as granulation liquid (Millili et al., 1996). The van der Waals energy of interaction (E) between two surfaces is dependent on the distance (h) between two surfaces–primary particles (Hiestand, 2002):

$$E = \frac{A_H}{12\pi h^2} \tag{1}$$

where A_H is the Hamaker constant. The Hamaker constant is function of the surface free energy of the solid particle and is, therefore, equal for all the pellet samples. The mechanical strength of the pellets studied here thus depends mainly on the interparticle distance as this quantity directly affects the work of adhesion between MCC particles. The finding that the tensile strength of agglomerate can be explained by the Griffith flaw theory supports this. This theory states that crack propagates, if the strain energy release rate exceeds the work of adhesion (Podczeck, 1998).

The work of Berggren and Alderborn has shown that resultant of the contraction driving force and the force counteracting contraction during drying defines the densification of the pellet. In the absence of osmotic pressure, capillary pressure constitutes the entire contraction driving force. The maximum capillary pressure (P_R) in the pore with hydraulic radius (r_H) is proportional to $\gamma_L \times \cos(\Theta)$ (Berggren and Alderborn, 2001):

$$P_R = \frac{\gamma_L \cos(\Theta)}{r_H} \qquad (2)$$

The values of the surface tension and contact angle of the granulation liquid with MCC, therefore, define the magnitude of the contraction driving force during drying. The dielectric constant of the granulation liquid is proportional to the reduction of the contraction counteracting force because it weakens long-range forces between MCC particles during agglomerate densification, thereby improving the repositioning propensity of the primary particles (Olsson et al., 1996; Berggren and Alderborn, 2001). On this basis, we propose that the product $\gamma_L \times \cos(\Theta) \times \varepsilon_R$ is proportional to the reciprocal values of the interparticle distances between the particles in the dry pellet.

2. Materials and methods

2.1. Preparation of pellets

Pellets were prepared by extrusion and spheronisation from MCC (AVICEL PH101, FMC, USA). Five sets of pellets were prepared, one from each of the following agglomeration liquids: purified water, anhydrous ethanol (MERCK, Germany) and mixtures of ethanol and water (4.9 mol%, 8.2 mol%, 21.1 mol% of ethanol).

The agglomeration liquid was added manually by pouring onto the dry powder of MCC (300 g) over a period of 5 min, while mixing the mass in a planetary mixer (PRS, Erweka, Heusenstamm, Germany) at level 3. The wetted mass was then wet mixed for 5 min at level 5. The agglomeration liquids were added in a proportion of 1.25 times the weight of the dry powder, except for purified water and anhydrous ethanol where ratios of 1.07 and 1.33 were used.

The wet powder mass was extruded at 60 rpm in an axial screen extruder (Pharmex 35T, Wysstec, Pery, Switzerland) equipped with a 1.2 mm thick screen with 1.0 mm diameter circular openings. The housing of the extruder was cooled with water at 18 °C. The extrudate was spheronised on a radial plate spheroniser (SPHEROMAT 250T, Wysstec, Pery, Switzerland). Extrudates prepared with the five liquids listed above were spheronised for 1.5 min at 950 rpm, 0.5 min at 750 rpm, 1.5 min at 900 rpm, 1.5 min at 900 rpm and 1 min at 850 rpm, respectively. Different proportions of granulation liquids and different spheronisation parameters were used in order to produce pellets of acceptable sphericity.

Sets of pellets were dried in a drier with forced convection (SO210, Elektromedicina, Niš, Yugoslavia) until 1–2% of residual granulation liquid was determined in a pellet sample using a balance with a drying unit (LP 16M/PM, Mettler-Toledo, Columbus, USA). Pellet samples produced using water, ethanol and ethanol/water mixtures were dried at 51.6 °C, 20.4 °C and 50.0 °C, respectively. Drying temperatures were determined empirically with the help of vapour pressure data for water and ethanol (Perry and Green, 1997), in order to achieve the same kinetics of mass evaporation of water and ethanol.

Size fractions of pellets between 0.710 mm and 1.000 mm were used for further characterization.

2.2. Characterization of surface free energy

Surface free energy contributions for MCC and the granulation liquids were determined by contact angle measurement using the Wilhelmy plate method with a Processor Tensiometer K12 controlled by K121.2 program (Krüss, Hamburg, Germany). The harmonic mean equation proposed by Wu, combined with Young's equation, was used to calculate surface free energy con-

tributions (Wu and Brzozowski, 1971):

$$4\left[\frac{\gamma_L^d\gamma_S^d}{\gamma_L^d+\gamma_S^d}+\frac{\gamma_L^p\gamma_S^p}{\gamma_L^p+\gamma_S^p}\right]=\gamma_L(1+\cos(\Theta)) \qquad (3)$$

where γ_L is the surface tension of the liquid, Θ is contact angle of a liquid on a solid surface and γ_L^d, γ_S^d, γ_L^p, γ_S^p are the dispersive and polar components of the surface free energy for the solid and liquid. A pair of nonpolar and polar liquid, i.e., 1-bromonaphthalene and glycerol (both from Riedel-De Haen, Germany) was used in measurements of contact angles in order to calculate the surface free energy contributions of MCC (Dalal, 1987). Prior to measuring contact angles, 300 mg samples of MCC were pressed into rectangular platelets for 30 s at 78.5 kN using hydraulic press (P/N 15011, Graseby Specac, Orpington, UK) and then stored for 24 h in a desiccator at 32% relative humidity. 1-Bromonaphthalene and bidistilled water were used in measurements of contact angles in order to calculate surface free energy contributions of a Teflon plate. Values of the surface tension and surface free energy contributions of standard liquids used in the assessment of values of the contact angles are given in Table 1. Contact angles were measured using the parameters of measurement given in Table 2. The result is the average of six measurements of advancing contact angle. After the values of the contact angles of the two liquids with the solid were known, a set of two equations (Eq. (3)) was then solved in order to determine the dispersive and polar components of the surface free energy of the solid.

Surface free energy contributions of the granulation liquids were obtained by measuring their surface tension and by determining the contact angle of the granulation liquid with the Teflon plate. The values of the surface tensions of the granulation liquids were as-

Table 2
Conditions of contact angle measurement

Parameters	Values
Velocity of the vessel until surface is found	30% of maximum velocity
Sensitivity of the surface detection	5×10^{-4} to 0.01 g
Velocity of the vessel during measurement	1.20 mm/min
Minimum difference between measuring points	0.05 mm
Depth of immersion	5–6 mm

sessed by the Wilhelmy plate method, using a standard platinum plate (Processor Tensiometer K12). The previously characterized Teflon plate is almost completely nonpolar, so the polar contribution to surface free energy can be neglected. Therefore, the dispersive component of the surface free energy of a given liquid was calculated from Eq. (3) using the data of the contact angle of the liquid with the Teflon plate and the surface tension of the granulation liquid. The polar component of the surface free energy was calculated assuming the additive nature of the polar and dispersive components of surface free energy (Eq. (4)) (Fowkes, 1964):

$$\gamma_L = \gamma_L^d + \gamma_L^p \qquad (4)$$

Contact angles were calculated for pairs of MCC and granulation liquids using their respective values of the surface free energy components (Eq. (3)).

2.3. Calculation of relative permittivity of granulation liquids

The values of the relative permittivities of the granulation liquids, at or near the temperatures of drying of the pellet samples, were calculated using literature data. Relative permittivities of water and ethanol were calculated using the model (Wohlfarth, 1996):

$$\varepsilon_R(T) = a + bT + cT^2 + dT^3 \qquad (5)$$

where ε_R is the relative permittivity at the given absolute temperature, T, and a, b, c and d are the parameters of the model (Table 3).

The values of the relative permittivities of water/ethanol mixtures were calculated using the follow-

Table 1
Surface tensions, dispersive and polar components of the surface free energy of standard liquids (all values at 20 °C, in mN/m)

Liquid	γ_L	γ_L^d	γ_L^p
Water[a]	72.8	21.8	51.0
Glycerol[b]	63.4	37.0	26.4
1-Bromonaphthalene[b]	44.6	44.6	0

[a] Della Volpe and Siboni (1997).
[b] Dalal (1987).

Table 3
Values of the model parameters of Eq. (5)

Liquid	a	b	c	d
Water[a]	0.24921×10^3	-0.79069×10^0	$+0.72997 \times 10^{-3}$	0
Ethanol[a]	0.15145×10^3	-0.87020×10^0	0.19570×10^{-2}	-0.15512×10^{-5}
Ethanol/water[b]	-0.52444×10^2	-0.24793×10^2	-0.5703×10^1	

[a] Wohlfarth (1996).
[b] Smith et al. (1998) at 333 K.

ing equations (Smith Jr. et al., 1998):

$$\varepsilon_{\text{ideal}} = x_E \varepsilon_{rE} + x_w \varepsilon_{rW} \qquad (6)$$

where $\varepsilon_{\text{ideal}}$ is the ideal relative permittivity of a water/ethanol mixture with mole fractions x_E, x_W of ethanol and water, respectively. ε_{rE} and ε_{rW} are the relative permittivities of pure ethanol and water calculated using Eq. (5).

$$\varepsilon_{\text{mix}} = \varepsilon_{\text{ideal}} + \varepsilon^E \qquad (7)$$

ε_{mix} is the relative permittivity of the mixture and ε^E, the excess permittivity calculated using Eq. (8) and values of parameters given in Table 3.

$$\varepsilon^E = x_W x_E (a + b(x_W - x_E) + c(x_W - x_E)^2) \qquad (8)$$

2.4. Assessment of tensile strength of pellets

Particle shape (roundness, aspect ratio, area) was determined using the following Image Analysis system: Q 500 MC (Leica Cambridge Ltd., Cambridge, UK) equipped with colour video camera TK-1280E (JVC, Japan) and a Leitz Labor Lux S microscope (Leica Microsystems, Heerbrugg, Switzerland). Particles were illuminated from below. Only pellets with roundness less than 1.2 and aspect ratio less than 1.1 were used to measure the tensile strength (Podczeck et al., 1999).

The tensile strengths of the pellets were determined using a modified breaking hardness tester DTSZM-200 (Chinoin Chemical and Pharmaceutical Works Ltd., Budapest, Hungary) at a crosshead speed of 20 mm/min. Forty-five pellets with known cross-section area were evaluated for each sample. The surface tensile strength was calculated using Eq. (9) and the data of the diametral crushing forces and cross-section areas:

$$\sigma_f(s) = \frac{0.4F}{\pi R^2} \qquad (9)$$

where $\sigma_f(s)$ is the surface tensile stress; F, the failure load; and R, the radius of the pellet. Pellets are brittle in nature, therefore, their tensile strength is variable. Weibull-analysis can be used in such cases to characterize a batch of nominally identical specimens. In this work, Weibull-analysis was performed using the numerical methodology described by Erck (Salako et al., 1998).

2.5. Assessment of disintegration time of pellets

The disintegration times of pellets were measured using a disintegration tester Erweka ZT4 (Erweka, Heusenstamm, Germany), which was modified by installing a 0.5 mm sieve at the bottom of the disintegration basket rack assembly. The procedure was further modified by using custom-made PMMA truncated cones without grooves. Standard disintegration discs were placed over truncated cones to intensify mechanical stress. The disintegration times of 100 mg pellet samples were determined in purified water at 36–38 °C. The disintegration time was set to the point at which no particles were present on the sieve in each disintegration basket. The results are the average of 8 or 12 disintegration times.

2.6. Assessment of friability of pellets

Friability test was conducted using a friability tester Erweka TA 10 (Erweka, Heusenstamm, Germany) in combination with an Erweka Abrasion Drum. A 10.00 g sample of pellets was put into the drum, together with 63 glass spheres of 5 mm diameter (10.13 g), and rotated for 10 min at 25 rpm. Glass spheres and pellet fragments were separated from stressed pellets using a set of sieves (2.000 mm, 0.400 mm). Powder that adhered to the pellet surface was removed by means of an air stream. The pellet sample was then again weighed and the friability calculated

(Eq. (10)). The result is the average of 3 runs:

$$\text{friability (\%)} = \frac{m_b - m_a}{m_b} \times 100 \qquad (10)$$

where m_b and m_a are the masses of pellets before and after the stress.

2.7. Assessment of pellet average pore diameter

Mean pore diameter of pellet sample was assessed by means of nitrogen adsorption and capillary condensation (Tristar 3000 Gas Adsorption Analyser, Micromeritics Instrument Co., Norcross, USA). Prior to analysis, samples of pellets were additionally dried in a vacuum drier at 90–100 °C overnight. The adsorption average pore diameter (d_p) was calculated using the data of single point adsorption total pore volume at $P/P_0 = 0.99$ (V) and five-point BET surface area (A_{BET}):

$$d_p = \frac{4V}{A_{BET}} \qquad (11)$$

2.8. Assessment of pellet porosity

Pellet porosity ($E_\%$) was calculated from the apparent particle density of the MCC powder (ρ_a) and the effective particle density of the pellets (ρ_e) using Eq. (12). The apparent particle density of the MCC particles was determined using a helium pycnometer (AccuPyc 1330 Pycnometer, Micromeritics Instrument Co., Norcross, USA). The effective pellet density of the pellets was determined by mercury porosimetry using a mercury porosimeter (Micromeritics Pore Sizer 9310, Micromeritics Instrument Co., Norcross, USA). Effective density was calculated from the sample weight and the sample volume at the initial mercury filling pressure:

$$E_\% = \left(1 - \left(\frac{\rho_e}{\rho_a}\right)\right) 100 \qquad (12)$$

2.9. SEM micrographs

Prior to analysis, pellets were immobilised by micromanipulation, and then coated with gold. Subsequently, SEM micrographs of pellets and pellet surfaces were taken with a scanning electron microscope (JEOL JXA 840A, JEOL Ltd., Tokyo, Japan).

3. Results and discussion

3.1. Surface tension and contact angle of granulation liquid with MCC

The surface properties of the granulation liquids and MCC were characterized by dynamic contact angle measurements. These results have then been used in calculation of contact angels of the granulation liquids with MCC (Eq. (3)), since direct measurement of contact angles was not possible due to the swelling problem. Surface tensions of the granulation liquids were measured using Wilhelmy plate method.

The results of contact angles of the standard liquids (Θ [°]) with Avicel PH101 and Teflon are given in Table 4. Measurement of contact angles of almost all the polar standard liquids, including water, with MCC is not possible as MCC swells during measurement, i.e., the geometry of compressed MCC plate changes significantly. The value of the measured contact angle of 1-bromonaphthalene with a Teflon plate is in accordance with published data (Fox and Zisman, 1950; Dalal, 1987). The value of the contact angle of glycerol on the Teflon plate is 4° higher than reported by Fox and Zisman (1950) and Dalal (1987) but in agreement with that of Jańczuk et al. (1989). The value of the contact angle of water with Teflon plate is 5° higher than that reported (Fox and Zisman, 1950; Dalal, 1987).

The calculated dispersive and polar components of surface free energy of Avicel PH101 and Teflon are given in Table 5. Surface free energy components were calculated using Eq. (3) and data from Table 4 and Table 1. The polar component of surface free energy of Teflon (γ_S^p) was calculated using the values of the contact angles obtained by 1-bromonaphtalene and water. Although the calculated value of γ_S^p of Teflon is 0.22 mN/m, the zero value of γ_S^p can be calculated within the standard deviation of the contact angle of

Table 4
Contact angles of standard liquids with Avicel PH101 and Teflon (Θ [°])

Liquid	1-Bromonaphthalene	Glycerol	Water
Solid			
Avicel PH101	16.9 ± 4.3	28.3 ± 2.9	*
Teflon	73.1 ± 1.4	104.0 ± 0.8	113.4 ± 1.3

Measured at liquid temperature $T = 20 \pm 0.1$ °C.

* Measurement not possible because of swelling of MCC.

Table 5
Calculated dispersive and polar components of surface free energy of solids (γ_S^d, γ_S^P [mN/m])

Solid	γ_S^d	γ_S^P
Avicel PH101	42.71	16.04
Teflon	21.24	0[*]

[*] Calculated using contact angles obtained by 1-bromonaphthalene and water.

water with Teflon. This indicates that Teflon can be regarded as a completely nonpolar material, in accordance with the literature (Dalal, 1987; Della Volpe and Siboni, 1997). If data of the contact angles of 1-bromonaphthalene and glycerol are used for calculating components of the surface free energy of Teflon, then a negative value of −1.41 mN/m is obtained for γ_S^p. This cannot be explained by the variation of contact angle obtained for glycerol. Therefore, this pair of contact angles was eliminated from calculation of the average value of γ_S^p of Teflon, as a negative value of γ_S^p is physically not possible.

The values of the surface tensions and the values of contact angles of granulation liquids with Teflon plate, together with the calculated surface free energy components of granulation liquids are reported in Table 6. Surface free energy components of the granulation liquids were calculated using Eq. (3), the contact angles data from Table 6 and surface free energy components data of Teflon from Table 5, assuming the value of γ_S^p of Teflon is zero. These calculations were necessary because data for γ_S^d and γ_S^p of the ethanol/water mixtures used are not available in the literature. Calculated values of γ_S^d and γ_S^p of ethanol and water are in accordance with literature data (Della Volpe and Siboni, 1997).

Contact angles of the granulation liquids on MCC can be calculated when the data of surface free energies for MCC and granulation liquids are known

(Tables 5 and 6). Calculated cosine of contact angles, relative permittivity of granulation liquids and values of the proposed product $\gamma_L \times \cos(\Theta) \times \varepsilon_R$ are given in Table 7.

When a value for $\cos(\Theta) > 1$ was calculated, the total spreading of granulation liquid was assumed and the $\cos(\Theta)$ was set to 1. Total spreading of the granulation liquid over MCC has been determined for all granulation liquids that have been used for pellet preparation, except for that of water. Relative permittivities of granulation liquids at or near the temperature of drying were obtained from the literature. The values of relative permittivities and calculated values of $\gamma_L \times \cos(\Theta) \times \varepsilon_R$ both decrease with increasing proportion of ethanol in the granulation liquid. There is an exception in case of 4.9 mol% ethanol/water mixture where the value of the proposed product is higher that in water. This leads to the suggestion that pellets produced using of 4.9 mol% ethanol/water mixture will have higher mechanical strength than those produced using water.

3.2. Characterization of pellets

The preparation procedure gave more or less spherical agglomerates - pellets. Extrusion time varied from 8 min to 30 min with ethanol wetted mass having the worst extrusion properties. Different drying temperatures were used to avoid the influence of drying kinetics on mechanical strength of the pellets. All the pellet samples were dried over 6–7 h to 1–2% of liquid content.

3.2.1. Tensile strength of pellets

Values of the tensile strength of the pellets increase with increase of the proposed product '$\gamma_L \times \cos(\Theta) \times \varepsilon_R$' (Tables 7 and 8, Fig. 1). Weibull-

Table 6
Surface tensions of granulation liquids (γ_L), contact angles of granulation liquids with Teflon platelet (Θ) and calculated components of liquid surface free energies (γ_L^d, γ_L^P)

Granulation liquids	Θ (°)	γ_L (mN/m)	γ_L^d (mN/m)	γ_L^P (mN/m)
Water	113.9 ± 1.2	71.5	21.3	50.2
Ethanol/water (4.9 mol%)	97.0 ± 0.5	47.0	20.0	27.0
Ethanol/water (8.2 mol%)	89.5 ± 1.0	40.0	19.2	20.8
Ethanol/water (21.1 mol%)	70.2 ± 1.2	30.0	19.1	10.9
Ethanol	31.4 ± 1.1	22.1	19.8	2.3

Measured at liquid temperature $T = 20 \pm 0.1\,°C$.

Table 7
Calculated cosine of contact angles ($\cos(\Theta)$), relative permittivities of granulation liquids (ε_R) and values of the product ($\gamma_L \times \cos(\Theta) \times \varepsilon_R$)

Granulation liquids	$\cos(\Theta)$	ε_R (T [°C])	$\gamma_L \times \cos(\Theta) \times \varepsilon_R$ (mN/m)
Water	0.475	69.4 (51.6)	2357
Ethanol/water (4.9 mol%)	1[*]	60.9 (60)	2862
Ethanol/water (8.2 mol%)	1[*]	57.3 (60)	2292
Ethanol/water (22.1 mol%)	1[*]	45.8 (60)	1374
Ethanol	1[*]	25.4 (20.4)	561.3

[*] Calculated values of $\cos(\Theta)$ are greater than 1 and were set to 1.

Table 8
Tensile strength of pellets ($n = 45$)

Granulation liquids—pellet types	σ_f (s) (MPa)	m	x_0 (MPa)	x_u	RMS (%)
Water	9.1 ± 1.4	7.33	9.77	0.000	24.6
Ethanol/water (4.9 mol%)	9.2 ± 1.3	7.40	9.80	0.000	17.9
Ethanol/water (8.2 mol%)	8.6 ± 1.1	8.29	9.21	0.000	24.5
Ethanol/water (21.1 mol%)	5.7 ± 0.9	6.82	6.09	0.000	15.3
Ethanol	0.61 ± 0.19	3.32	0.686	0.000	26.4

m, Weibull-modulus; RMS, root mean square deviation (residual analysis); σ_f (s), surface tensile stress; x_0, characteristic pellet strength; x_u, plasticity term.

analysis was performed in order to correctly interpret tensile strength measurement data (Salako et al., 1998). The characteristic strength value of the pellet batch (x_0) quantifies the stress for 63.2% probability of failure. The relationship between the characteristic strength values of the pellet samples and $\gamma_L \times \cos(\Theta) \times \varepsilon_R$ is similar to that of the arithmetic means of tensile strengths. Values of the characteristic strengths of the pellet samples are proportionally higher when compared to the mean tensile strength values of the same pellet sample (Table 8). The Weibull modulus m is a measure of the variability of the failure properties of
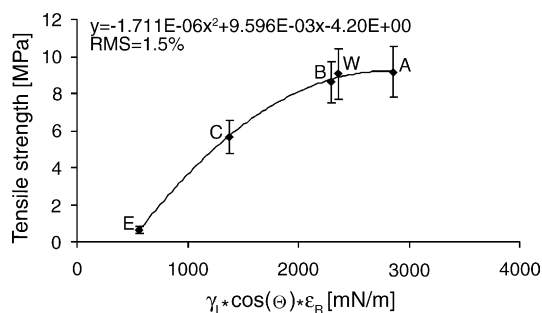
a pellet sample. The lower the modulus the more brittle the pellet sample. The Weibull modulus m increases with an increase in the value of $\gamma_L \times \cos(\Theta) \times \varepsilon_R$, with the exception of the sample prepared using 8.2 mol% ethanol/water mixture (Table 8). A polynomial function of second order can be fitted to the experimental points of tensile strength (Fig. 1). Although the correlation between the tensile strength of the pellets and $\gamma_L \times \cos(\Theta) \times \varepsilon_R$ is not linear, there is no experimental point that would deviate from expected sequence of data points. Values of the characteristic pellet strength also indicate that the pellet samples prepared with water and with 4.9 mol% ethanol/water mixture are the same in terms of tensile strength. This could be explained as a consequence of the limited agglomerate densification during drying, when interparticle distances become sufficiently small for the high mechanical friction between particles to limit further densification. Similarity of the two samples could further be explained by suggesting that the cohesive properties of MCC become a limiting factor in this range of tensile stress.

Fig. 1. Surface tensile stress of pellets (σ_f(s)) prepared with different granulation liquids as function of $\gamma_L \times \cos(\Theta) \times \varepsilon_R$; W: water; E: ethanol; A: ethanol/water (4.9 mol%); B: ethanol/water (8.2 mol%); C: ethanol/water (21.1 mol%).

3.2.2. Disintegration time of pellets

Disintegration time of the pellets increases with increase in the value of $\gamma_L \times \cos(\Theta) \times \varepsilon_R$ (Fig. 2). Although the disintegration times of pellets are proportional to $\gamma_L \times \cos(\Theta) \times \varepsilon_R$, the disintegration time
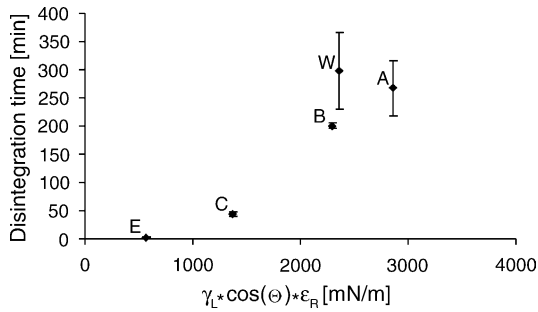
Fig. 2. Disintegration time of pellets prepared using different granulation liquids as function of $\gamma_L \times \cos(\Theta) \times \varepsilon_R$; W: water; E: ethanol; A: ethanol/water (4.9 mol%); B: ethanol/water (8.2 mol%); C: ethanol/water (21.1 mol%).

of pellets produced with water deviates from this sequence. When considering standard deviation of disintegration times for pellets produced with water and pellets produced with the use of 4.9 mol% ethanol/water mixture there is no significant difference between both disintegration times ($\alpha = 0.05$). The disproportionately large disintegration time of pellets produced with water could be a result of a mechanical interweaving of cellulose chains as MCC particles swell during wet agglomeration. Swelling, and, therefore, the interweaving of MCC, occurs to a greater extent in the case of water than with ethanol.

3.2.3. Friability of pellets

Friability of pellets decreases with increase in the value of $\gamma_L \times \cos(\Theta) \times \varepsilon_R$ (Fig. 3). For the experimental points A, W, B, and C, we can observe almost a linear change of pellet friability with change of the
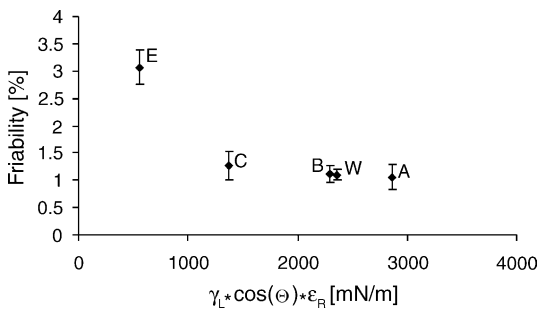
$\gamma_L \times \cos(\Theta) \times \varepsilon_R$ value, when experimental point E exhibits a much higher friability that is not linearly proportional to the other experimental points. On the other hand, the function friability $= 0.9624 + 6.620 \times 10^5 (\gamma_L \times \cos(\Theta) \times \varepsilon_R)^{-2}$ (RMS $= 2.2\%$) can be fitted to experimental points which is in agreement with the negative linear relation between average pore diameter of the pellets and $\gamma_L \times \cos(\Theta) \times \varepsilon_R$ (Fig. 4) and the equation of van der Waals energy of interaction (Eq. (1)). Therefore, a positive linear relation can be obtained when plotting friability data against the inverse values of $(\gamma_L \times \cos(\Theta) \times \varepsilon_R)^2$. Lack of experimental points between experimental point E and C (Fig. 3) reduces the certainty of the proposed model.

3.2.4. Average pore diameter of pellets

The value of the average pore diameter of pellet samples decreases linearly with an increase in the value of $\gamma_L \times \cos(\Theta) \times \varepsilon_R$ (Fig. 4). Mesopores were evaluated in the range from 1.7 nm to 300 nm. All samples were subjected to additional drying in a vacuum dryer at 90–100 °C prior to analysis to avoid small quantities of liquid present in the agglomerate from hindering the measurement. Although the temperature of drying is relatively high, the net change in pellet structure should be small, as the liquid content of the pellets was less than 2% after manufacture and the pellet samples were then stored in closed containers with desiccant. The data obtained are, therefore, at least of comparative value. We were not able to evaluate a sample of pellets produced with 4.9 mol% ethanol/water mixture as the apparatus failed to assess BET surface area of
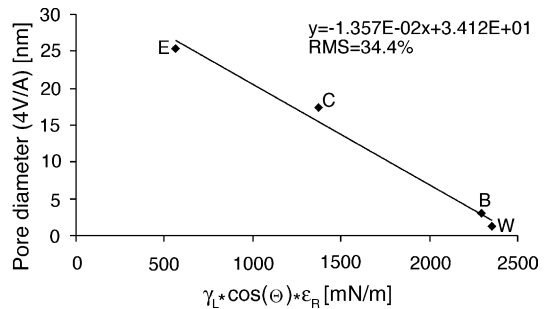

Fig. 3. Friability of pellets prepared using different granulation liquids as function of $\gamma_L \times \cos(\Theta) \times \varepsilon_R$; W: water; E: ethanol; A: ethanol/water (4.9 mol%); B: ethanol/water (8.2 mol%); C: ethanol/water (21.1 mol%).

Fig. 4. Adsorption average pore diameter (4 V/A) of pellets prepared using different granulation liquids as function of $\gamma_L \times \cos(\Theta) \times \varepsilon_R$; W: water; E: ethanol; B: ethanol/water (8.2 mol%); C: ethanol/water (21.1 mol%).

Table 9
Apparent density (ρ_a) of Avicel PH101 and effective density (ρ_e) of some pellet types with calculated porosity ($E_\%$)

Granulation liquids—pellet types	ρ_e (g/cm)	$E_\%$ (%)
Water	1.3639	13.9
Ethanol/water (4.9 mol%)	1.3865	12.5
Ethanol	0.7480	52.8

Apparent density of MCC (ρ_a [g/cm^3]): 1.5837 ± 0.0008.

the sample. The reason could lie in the lower limit of the pore size that can be evaluated and the fact that pellets produced with water have an average pore diameter close to this limit. Our calculations predict that pellets produced with 4.9 mol% ethanol/water mixture have pores of even lower diameters than those prepared with water.

Although we have to be aware of the assumption of pores having the cylindrical shape, which is used in the calculation of the average pore diameter (Eq. (11)), we must point out that the values of the assessed average pore sizes are in the range where van der Waals forces changes significantly. The net change in cap-

illary force due to atmospheric water condensation is small in the range of pores observed for the pellet samples compared with the change of van der Waals force in the same size range (Podczeck, 1998). Results of the average pore diameter assessment, therefore, supports the correlations between the product $\gamma_L \times \cos(\Theta) \times \varepsilon_R$ and the mechanical properties of the investigated pellets as their bonding mechanism is based mainly on van der Waals interactions.

3.2.5. Porosity of pellets

The porosity of pellets produced with ethanol is substantially higher then those of pellets produced with water and 4.9 mol% ethanol/water mixture (Table 9). Difference between porosities of pellets produced with water and 4.9 mol% ethanol/water mixture exists, with pellets produced with water being more porous. This supports the idea of porosity of pellets being in proportion to the value of $\gamma_L \times \cos(\Theta) \times \varepsilon_R$. The porosity values of the three samples are consistent with the literature finding of agglomerate porosity being inversely proportional to its tensile strength (Podczeck, 1998).
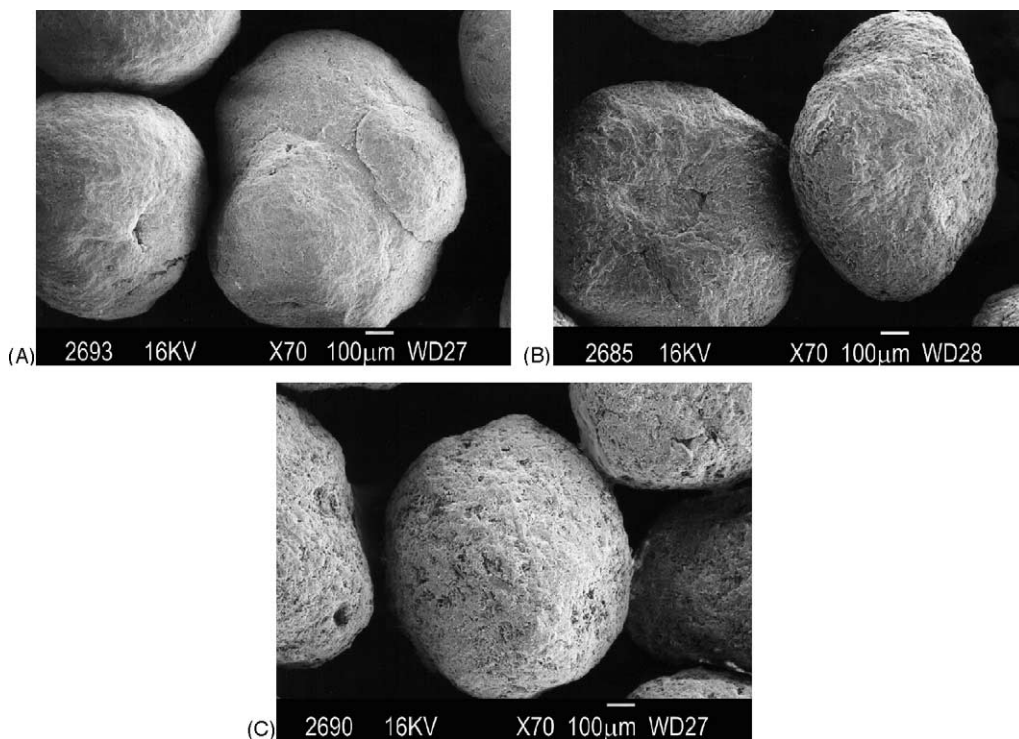

Fig. 5. Micrographs of pellets produced with A: water; B: ethanol/water (4.9 mol%); C: ethanol.

Due to non-uniform distribution of the values of the porosities we are not able to completely confirm this finding.

3.2.6. Shape and surface of the pellets

There is no considerable difference in the shape of pellets produced with the various granulation liquids (Fig. 5A–C). The lack of sphericity observed for all pellet samples can be attributed to the arbitrary times and frequencies of spheronisation that have been kept as close as possible for all the granulation liquids. However, we were still able to find pellets with aspect ratio less than 1.1 in all pellet samples when preparing pellets for tensile strength analysis.

Surface roughness and density of the pellet sample produced with ethanol (Fig. 6C) are clearly different from those represented by pellet samples produced with water or 4.9 mol% ethanol/water mixture (Fig. 6A and B). Large pores and separate primary particles of MCC can be observed on the surface of the pellet produced with ethanol (Fig. 6C). While dense surfaces with no pores are observed with pellets produced with water and 4.9 mol% ethanol/water mixture (Fig. 6A and B), there is a noticeable difference in surface roughness of the two types of pellets, the water pellet having the smoother surface.

Difference in surface properties of the pellet samples can be attributed partially to the difference in values of the proposed product $\gamma_L \times \cos(\Theta) \times \varepsilon_R$, but also to differences in the swelling of MCC when exposed to water, ethanol or ethanol/water mixture. A suggestion of the mechanical interweaving of partially solvated MCC chains is supported by the SEM micrograph (Fig. 6A), where almost none of the separate primary MCC particles are observed. A uniform solid surface was formed, due to the rotor plate strain and mobility of partially solvated MCC chains during the spheronisation process.

3.3. The significance of the relative permittivity

The relative permittivity of the granulation liquid was incorporated in the product $\gamma_L \times \cos(\Theta) \times \varepsilon_R$ be-
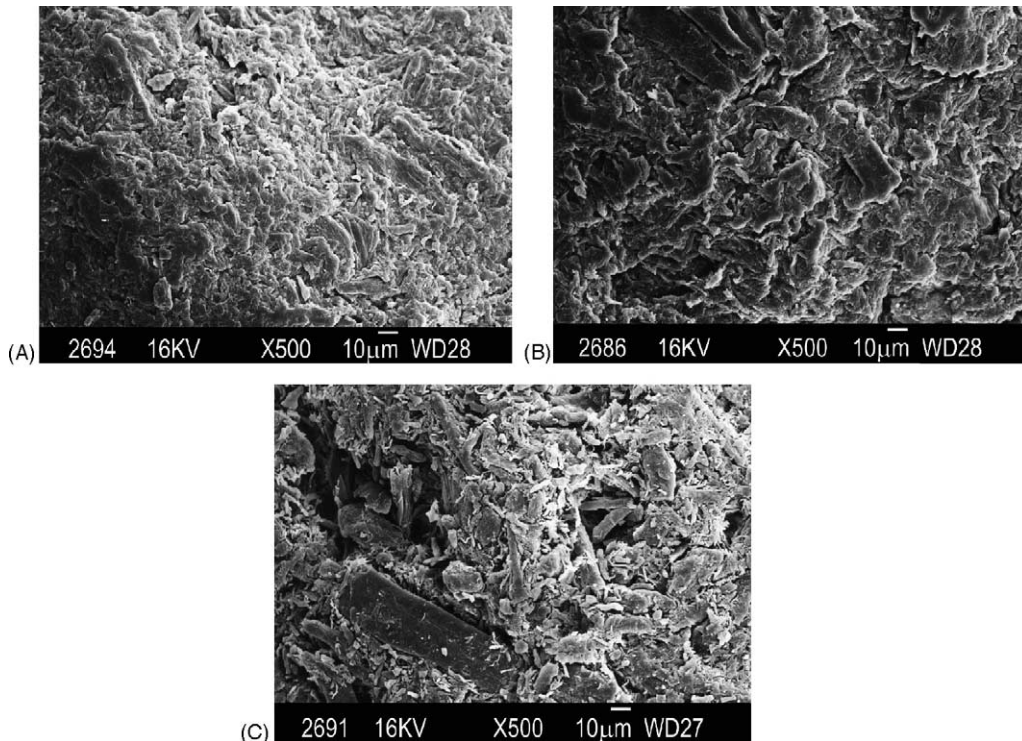

Fig. 6. Surface details of pellets produced with A: water; B: ethanol/water (4.9 mol%); C: ethanol.

cause it is proportional to the reduction of the contraction counteracting force. The reduction is explained with weakening of the long-range forces between MCC particles during agglomerate densification.

If the product $\gamma_L \times \cos(\Theta)$ is used in correlations with the mechanical properties of the pellet samples, the experimental point of pellets produced with water shifts between the experimental points of the pellets produced with 8.2 mol% and 21.1 mol% ethanol/water mixtures. Experimental points of pellets, other than those produced with water, retain similar positions as in Figs. 1–4. As a consequence no correlations or expected sequences of data points are observed when plotting the data of tensile strength, friability, disintegration time and average pore diameter as a function of the product $\gamma_L \times \cos(\Theta)$. This finding confirms the incorporation of the relative permittivity of the granulation liquid in the proposed product.

4. Conclusions

The values of tensile strength and disintegration times of the group of pellet samples studied increase with increase of the proposed product '$\gamma_L \times \cos(\Theta) \times \varepsilon_R$', while the values of friability, average pore diameter and porosity decreases. Although the relations between the aforementioned quantities are, in general, not linear, the expected sequences of plotted data points support the idea of correlating the proposed factor '$\gamma_L \times \cos(\Theta) \times \varepsilon_R$' with mechanical properties of the pellets. The idea of correlating is further supported by the linear relation between average pore diameter and $\gamma_L \times \cos(\Theta) \times \varepsilon_R$. Tensile strength and disintegration time of pellets produced with 4.9 mol% ethanol/water mixture are equal to those of pellets produced with water, however, their friability and porosity are lower than or at least equal to those of pellets produced with water. These findings are in agreement with the idea that pellets produced with a granulation liquid with higher $\gamma_L \times \cos(\Theta) \times \varepsilon_R$ value will have also greater mechanical strength.

Therefore, the suggestion of a product $\gamma_L \times \cos(\Theta) \times \varepsilon_R$ supports the theory that granulation liquid influences mechanical and structural properties of the pellets through the contraction driving and contraction counteracting forces during drying.

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