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International Journal of Pharmaceutics 207 (2000) 77–88

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

The utilization of surface free-energy parameters for the selection of a suitable binder in fluidized bed granulation

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Received 19 June 2000; received in revised form 1 August 2000; accepted 1 August 2000

Dedicated to Professor Dr Peter C. Schmidt at the occasion of his 60th birthday.

Abstract

Surface free energy was determined for model substances pentoxyfilline, acyclovir, lactose and binding agents (that were used in the granulation process) hydroxypropilmethyl cellulose (HPMC) and polyvinylpyrrolidone (PVP) were determined by contact angle measurements. The methods of Wu, Good–van Oss and Della Volpe were used for solid-surface free-energy calculation. Spreading coefficients (S) were calculated and correlated with granulate properties. Granulates consisted of model drug and binding agent, and were produced in fluid bed granulator Glatt powder coater granulator GPCG1 by means of spraying the colloidal solution of binder on the model substance. Granules contained either 5% or 10% binder. Inverse granules, however, were also produced by spraying the model drug (i.e. pentoxyfilline and lactose) on the binding agent (HPMC, PVP). Particle size distribution, friability, true density, bulk density and tapped density of the granulates were determined. Although many different parameters influence the granule properties, it has been found that the interactions between the drug and the binder play a very important role. Spreading coefficients were found to be in good correlation with the friability of granulates. Positive spreading coefficient values of the binder over the model substance correlate well with the low friability of the granules containing lower amount of binder, i.e. 5%. In the group of the same binder, the spreading coefficient values decrease from pentoxyfilline over lactose to acyclovir. Friability results show that, for the system under consideration, PVP offers certain advantages over the grade of HPMC employed. The increase of the binder amount from 5 to 10% resulted in more friable granulates. Lower work of cohesion of the binder (PVP and HPMC) than the work of adhesion between binder and the model substances is considered responsible for the higher friability of the granules. The inverse granulation process, where the suspension of the model substance was sprayed over the solid binder particles, proved more efficient with HPMC than with PVP. According to the spreading coefficient results, the binder should spread over the drug. However, the kinetics of wetting appears to play an important role in the granulation process. According to these results, the conclusion was made that water wets HPMC much faster than PVP.

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0378-5173/00/$ - see front matter
PII: S0378-5173(00)00535-4

Keywords: Contact angle; Surface free energy; Spreading coefficient; Fluid bed granulation; Granulate properties

1. Introduction

Granulation is a process that is used for improvement of flow and compression behavior of drugs and excipients. Fluidized bed granulation, an often-used technique in pharmaceutical industry, proceeds by simultaneous solvent liquid addition and solvent evaporation (Swarbrick and Boylan, 1993). Many factors may affect the outcome of a wet granulation process. They can be divided into process variables (inlet air temperature, outlet air temperature, inlet air humidity, size of the expansion chamber, etc.) and variables of the entering materials (particle size distribution, physicochemical properties; among them also surface free energy, binder solution concentration, etc.). Under condition that optimal process parameters are selected, spreading of the binder over the substrate, binder–substrate adhesion and binder cohesion, are the main parameters that influence optimum granulation (Krycer et al., 1983). The aim of this work was to find out if it is possible to correlate the granule properties produced in the top-spray fluid bed granulator with spreading coefficients calculated from solid-surface free-energy parameters of the included substances.

2. Solid-surface free energy and spreading coefficient

Surface free energy is an important physicochemical property of a solid that can be assessed indirectly from wettability measurements. Several calculation methods for solid-surface free energy (γ_s) are available. According to the method of Wu (1971), surface free energy is a sum of polar (p) and dispersion (d) components. Solid-surface free energy can be assessed by contact angle measurement of two liquids of known polarity and can be assessed by solving two equations with two unknowns (Eq. (1)).

$$(1+\cos\theta)\gamma_l = \frac{4(\gamma_s^d \times \gamma_l^d)}{\gamma_s^d + \gamma_l^d} + \frac{4(\gamma_s^p \times \gamma_l^p)}{\gamma_s^p + \gamma_l^p} \quad (1)$$

where γ_l is the liquid surface tension and γ_s the solid surface free energy.

On finding that all systems cannot be described by means of Wu's method, Good and van Oss upgraded it (van Oss et al., 1987, 1988). It also divides surface free energy into polar (AB) and nonpolar (Lifshitz–van der Waals (LW)) parts, and the surface free energy is the sum of these parts. The polar part (AB) is further divided into electron donor (base γ^-) and electron acceptor (acid γ^+) parameters. The acid–base (AB) component of surface free energy is estimated from Eq. (2) and the surface free energy from Eq. (3). The contact angle of the three liquids of known surface tension components must be used for determining the three unknown components of the solid surface free energy (γ_s^{LW}, γ_s^+ and γ_s^-). Thus, three equations of the type of Eq. (3) must be solved simultaneously.

$$\gamma = 2\sqrt{\gamma^+ \cdot \gamma^-} \quad (2)$$

$$(1+\cos\theta)\gamma_l = 2\left(\sqrt{\gamma_s^{LW}\gamma_l^{LW}} + \sqrt{\gamma_s^+\gamma_l^-} + \sqrt{\gamma_s^-\gamma_l^+}\right) \quad (3)$$

The problem of the Good–van Oss method lies in the fact that electron acceptor and electron donor parameters of any liquid or solid cannot be measured. In this method, water is selected as the standard with equally strong electron acceptor as electron donor parameters ($\gamma^+ = \gamma^- = 25.5$ mN/m). Recently, Della Volpe argued with this postulate, because literature data show that surfaces have base components systematically greater than the acid components, so they generally 'seem' to be much more basic than acidic (Della Volpe and Sibioni, 1998). For this reason, Della Volpe suggested the use of the 'solvatochromic' scale where water is considered an electron acceptor or Lewis acid 6.5 times stronger than electron donor or Lewis base. Different choice of reference electron donor and electron acceptor values for water results in different values for all other liquids that are used for contact angle measurements (Della Volpe and Sibioni, 1998).

When solid-surface free-energy parameters are known, the spreading coefficient (S) may be calculated to predict the interactions of binder with a substrate. During wet granulation, spreading of binder over a powder mass is preferred. The spreading coefficient is the measure of the spreading degree of one substance over another and is calculated as a difference of work of adhesion (W_a) and work of cohesion (W_c). The spreading coefficient of a binder over the substrate (S_{12}) or substrate over the binder (S_{21}) can be calculated. These calculations can be carried out according to the methods of Wu (Eqs. (4) and (5)), Good–van Oss (Eqs. (6) and (7)) and Della Vople (Eqs. (6) and (7)).

$$S_{12} = 4\left[\frac{\gamma_1^d\gamma_2^d}{\gamma_1^d+\gamma_2^d}+\frac{\gamma_1^p\gamma_2^p}{\gamma_1^p+\gamma_2^p}-\frac{\gamma_1}{2}\right] \quad (4)$$

$$S_{21} = 4\left[\frac{\gamma_1^d\gamma_2^d}{\gamma_1^d+\gamma_2^d}+\frac{\gamma_1^p\gamma_2^p}{\gamma_1^p+\gamma_2^p}-\frac{\gamma_2}{2}\right] \quad (5)$$

$$S_{12} = \gamma_2-\gamma_1-((\sqrt{\gamma_1^{LW}}-\sqrt{\gamma_2^{LW}})^2 + 2(\sqrt{\gamma_1^+\gamma_1^-}+\sqrt{\gamma_2^+\gamma_2^-}-\sqrt{\gamma_1^+\gamma_2^-}-\sqrt{\gamma_1^-\gamma_2^+})) \quad (6)$$

$$S_{21} = \gamma_1-\gamma_2-((\sqrt{\gamma_1^{LW}}-\sqrt{\gamma_2^{LW}})^2 + 2(\sqrt{\gamma_1^+\gamma_1^-}+\sqrt{\gamma_2^+\gamma_2^-}-\sqrt{\gamma_1^+\gamma_2^-}-\sqrt{\gamma_1^-\gamma_2^+})) \quad (7)$$

3. Materials and methods

The model substances used were lactose (DMV International, Netherlands), pentoxyfilline (KRKA d.d., Slovenia), acyclovir (LEK d.d., Slovenia), and binders hydroxypropymethylcellulose (HPMC) (Syntapharm, Germany) and polyvinylpyrrolidone (PVP) (BASF, Germany). Liquids used for wetting assessment were: bidistilled water, glycerol (Riedel-de Haën AG, Germany), diiodomethane (Sigma Germany), *n*-hexane (Kemika Zagreb, Croatia), heptane (Riedel-de Haën AG, Germany), *n*-propanol (Riedel-de Haën AG, Germany), 1-butanol (Merck, Germany) and 1-octanol (Merck, Germany).

3.1. Wetting measurements

Compacts of the powder (200 mg) were prepared in a highly polished stainless steel punch and die assembly (2.5×10 mm) in a Specac (England) hydraulic press with a 10 s dwell time and at a pressure of 2×10^8 Pa. The exact perimeter of the plates was measured using a micrometer. The contact angle of the liquids was determined by means of the Wilhelmy plate technique using a Krüss Tensiometer K12 (Germany). Temperature was controlled at 20 ± 0.5°C, by flowing water from a circulator (Haake, Germany). The test liquid (water, diiodomethane and glycerol) was placed in a clean glass dish and raised by means of a motorized platform to contact the powder plate. The platform was raised at the speed of 1.2 mm/min. From the force measurements, the contact angle was obtained using Krüss tensiometer software (Krüss GmbH, 1996). The experimental technique is described elsewhere (Buckton and Newton, 1985)

Wetting of the powders was determined also by means of a liquid penetration method with the use of Krüss Tensiometer K12. The penetrating liquids were hexane, heptane, *n*-propanol, *n*-butanol and 1-octanol. The use of water was not possible, because it did not penetrate into samples. The powders were packed into glass tubes using of a tapped density apparatus for 10 min (VanKel, USA). The tube was cold silanized to prevent preferential wetting of the glass during measurements (Mohammad and Fell, 1982)

3.2. Production of granules

Granules were prepared from powders as received. The particle size distribution and average size of the powders were measured using a laser diffraction technique (Mastersizer S, MSX 64 Dry Powder Feeder; Malvern Instruments, Worcs., England). The median size of the powders is listed in Table 1.

A fluidized bed granulator (GPCG1; Glatt, Germany) with a top-spray container was used for granulation. A 5% suspension of the binder (PVP and HPMC) in water was prepared in a glass vessel by heating and stirring. The model

Table 1
The median size of the powders used in fluidized bed granulation

Powder	Median particle size (μm)
PVP	193
HPMC	78
Lactose	66
Acyclovir	16
Pentoxyfilline	27

substance (acyclovir, pentoxyfilline or lactose; Table 2) was introduced into the conical container and fluidized from below by a stream of air. Final granules contained 5 or 10% binder. Inverse granulates were produced by way of spraying the water solution containing the model substance over the dry binder. The operating conditions adopted in fluidized bed granulator were as follows:

Feed load	300 or 400 g powder (Table 2)
Volume	300–600 ml (Table 2)
Rate of binder solution sprayed	10–13 ml/min
Atomizing air pressure	1.5 bar
Inlet air temperature	50°C
Filter shaking interval	10 s
Duration of filter shaking	3 s
Relative humidity of inlet air	40%
Drying time	10 min

The air inlet was adjusted by opening a flap. Granulation was monitored visually by airflow adjustment during agglomeration with a constant flow pattern of the particles that grow and become heavier. Temperature of the product during agglomeration was maintained between 23 and 30°C. When the granulating fluid was consumed, the product was dried for 10 min at a temperature between 43 and 46°C.

3.3. Particle size

The granules were sized by shaking in a test sieve shaker (Vibrations-Prüfsiebmaschine Thyr 2 MLW; Ilmenau, Germany) for 15 min. Size fractions of <200, 200–400, 400–630, 630–800,

Table 2
The composition of the granulates used in the work

Sample label	Model substance	Binder	m(model substance) (g)	m(binder) (g)	m(binder solution) (g)
LAC-PVP5	Lactose	PVP	400	20	400
LAC-PVP10	Lactose	PVP	300	30	600
LAC-HPMC5	Lactose	HPMC	400	20	400
LAC-HPMC10	Lactose	HPMC	300	30	600
ACY-PVP5	Acyclovir	PVP	300	15	300
ACY-PVP10	Acyclovir	PVP	300	30	600
ACY-HPMC5	Acyclovir	HPMC	300	15	300
ACY-HPMC10	Acyclovir	HPMC	300	30	600
PEN-PVP5	Pentoxyfilline	PVP	300	15	300
PEN-PVP10	Pentoxyfilline	PVP	300	30	600
PEN-HPMC5	Pentoxyfilline	HPMC	300	15	300
PEN-HPMC10	Pentoxyfilline	HPMC	300	30	600
PVP-LAK5[a]	PVP	Lactose	300	15	300
PVP-PEN5[a]	PVP	Pentoxyfilline	300	15	300
HPMC-LAK5[a]	HPMC	Lactose	300	15	300
HPMC-PEN5[a]	HPMC	Pentoxyfilline	300	15	300

[a] Inverse granules.

Table 3
Contact angle values, θ (deg.), for liquids on solid plates of model materials

Solid surface	Water	Glycerol	Diiodomethane
PVP	75.3 ± 2.3	55.5 ± 0.7	40.5 ± 1.8
HPMC	83.3 ± 0.9	75.7 ± 0.6	44.2 ± 0.7
Lactose	41.8 ± 1.0	32.9 ± 2.1	32.8 ± 2.4
Acyclovir	52.0 ± 0.7	45.7 ± 2.5	34.5 ± 1.8
Pentoxyfilline	46.5 ± 0.7	54.5 ± 0.7	22.4 ± 2.2

800–100, 100–1250, 1250–1600 and >1600 μm were collected.

3.4. Friability

There is no official procedure for the testing of granulates friability. For this reason the method was adopted from the literature (Zajič and Buckton, 1990) and modified so that glass balls were used for abrasion of the granules instead of steel balls. A 5 g fraction of the granulate that gave more than 80% of batch mass was weighted into a 67 ml plastic chamber together with ten glass balls ($m = 5$ g) with a diameter of 10 mm. Four plastic chambers were put into a friabilator (Erweka, Germany) for 10 min at a rotating speed of 20 rpm. The abraded samples were shook on the sieve with the lower mesh size of the particle size fraction that was used for the test. Results are presented as a mass loss in the percentage of total weight.

3.5. True density

True density was measured using a helium pycnometer (Mycromeritics Accupyc 1330, USA). Results are averages of five replicate determinations.

3.6. Bulk density

Sample was gently passed into a 100 ml graduated cylinder to the 100 ml mark and weighed. From the mass and volume data, the bulk density was calculated. Results are averages of three replicate determinations.

3.7. Tapped bulk density

The same sample used for bulk density measurement was subjected to a tapped density tester (Vankel, USA). A total of 1500 taps with the displacement amplitude of 14 mm were used for the determination. Results are averages of three replicate determinations.

4. Results and discussion

The reproducibility of contact angle results is in the range of $\pm 2.5°$. Results are listed in Table 3. According to the literature data among appropriate liquid contact angle combinations that are suitable for surface free-energy calculation by means of the methods of Wu, Good–van Oss and Della Volpe are also combinations water/diiodomethane and water/glycerol/diiodomethane (Dalal, 1987; Della Volpe and Sibioni, 1998). By use of these liquid combinations, the solid-surface free energy (γ_s) was assessed and the results (Table 4) used for calculations of spreading coefficients. Surface-tension components of liquids that were used for solid surface free energy calculation are listed in Table 5.

Spreading coefficients of both binders (PVP, HPMC) over the substrates (lactose, acyclovir, pentoxyfilline) and those of substrates over the binders were calculated in order to predict the properties of granulates. As stated by Rowe (1989), one can expect the formation of dense nonfriable granules when the spreading coefficient of a binder over the substrate S_{12} is positive. In the case when the spreading coefficient S_{12} is negative and S_{21} positive, the substrate adheres to the binder at isolated points. In this second type of granules, the binder does not form a film around the substrate particles, which causes the formation of more open porous structure of granules (Rowe 1989).

From Fig. 1, it can be seen that the increase of the binder amount in the formulation, from 5 to 10%, results in an increase in granule diameter.

Results show that the spreading coefficient of PVP and HPMC over the substrate (S_{12}) is always positive and that of the substrate over the binder

(S_{21}) negative. For both binders, the highest spreading coefficient value (S_{12}) was observed with pentoxyfilline and the lowest with acyclovir. Prediction from our results is therefore that all model substances (substrates) under consideration, i.e. pentoxyfilline, acyclovir and lactose, would form granules with low friability with both binders.

Friability results show good compliance with the predictions on the basis of spreading coefficient when granules with 5% of binder added are compared (Tables 6 and 7, and Fig. 2).

When granules with the same binder (PVP or HPMC) are compared, it can be seen that pentoxyfilline forms less friable granulates than lactose and acyclovir, which correlates well with the

Table 4
Surface free energy of used binders and model materials

	γ (mN/m)	PVP	HPMC	Lactose	Acyclovir	Pentoxyfilline
Wu[a]	γ_s^d	39.9	38.2	43.3	42.6	47.1
	γ_s^p	10.5	7.5	26.1	21.2	30.0
	γ_s	50.4	45.7	69.4	63.6	77.1
Good–van Oss[b]	γ^{LW}	39.4	37.4	43.0	42.3	47.0
	γ^{AB}	4.9	1.0	14.2	8.9	9.2
	γ^+	1.6	0.04	1.9	0.9	0.36
	γ^-	3.8	6.0	26.4	22.0	58.3
	γ_s	44.3	58.4	57.2	51.2	56.2
Della Volpe[c]	γ^{LW}	39.4	37.4	43.0	42.3	47.0
	γ^{AB}	5.3	2.2	12.3	5.5	21.5
	γ^+	6.4	1.2	3.3	0.75	5.5
	γ^-	1.1	3.7	11.3	10.2	209
	γ_s	44.6	41.6	55.3	47.8	68.5

[a] Zajič and Buckton (1990).
[b] Van Oss et al. (1997).
[c] Della Volpe and Sibioni (1998).

Table 5
Surface tension components of liquids used for solid surface free energy calculation

	γ (mN/m)	Water	Diiodomethane	Glycerol
Wu[a]	γ_l^d	21.8	50.4	32.0
	γ_l^p	50.2	0	31.7
	γ_l	72.0	50.4	63.7
Good–van Oss[b]	γ^{LW}	21.8	50.8	34.0
	γ^{AB}	51.0	0	30.0
	γ^+	25.5	0	3.92
	γ^-	25.5	0	57.4
	γ_l	72.8	50.8	64.0
Della Volpe[c]	γ^{LW}	21.8	50.8	34.4
	γ^{AB}	51.0	0	29.6
	γ^+	65.0	0	16.9
	γ^-	10.0	0	12.9
	γ_l	72.8	50.8	64.0

[a] Zajič and Buckton (1990).
[b] Van Oss et al. (1997).
[c] Della Volpe and Sibioni (1998).

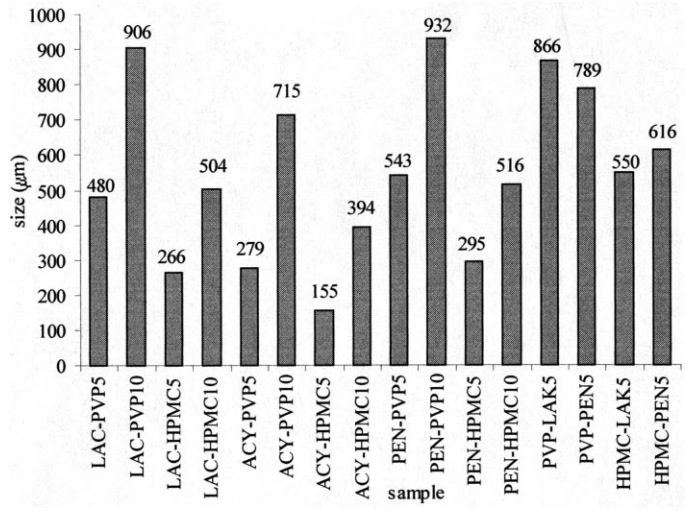

Fig. 1. Average size of the granules (μm).

Table 6
The spreading coefficients of the PVP over the drug (S_{12}) and drug over PVP (S_{21}) calculated according to the methods of Wu, Good–van Oss and Della Volpe

Drug (2)	PVP (1)					
	Wu		Good–van Oss		Della Volpe	
	S_{12}	S_{21}	S_{12}	S_{21}	S_{12}	S_{21}
Lactose	12.2	−25.8	12.1	−13.7	13.9	−7.5
Acyclovir	9.7	−17.1	8.6	−5.2	11.4	−7.9
Pentoxyfilline	16.7	−36.7	19.0	−4.6	24.8	−34.2

Table 7
The spreading coefficients of the HPMC over the drug (S_{12}) and drug over HPMC (S_{21}) calculated according to the methods of Wu, Good–van Oss and Della Volpe

Drug (2)	HPMC (1)					
	Wu		Good–van Oss		Della Volpe	
	S_{12}	S_{21}	S_{12}	S_{21}	S_{12}	S_{21}
Lactose	13.1	−34.3	13.3	−24.3	11.4	−16.0
Acyclovir	11.3	−24.9	9.3	−16.3	6.6	−10.9
Pentoxyfilline	17.0	−45.8	13.1	−22.4	19.7	−33.9

observed spreading coefficient for both binders over that substrate (Figs. 3–5). Highest friability of granules with acyclovir is in good correlation with the lowest spreading coefficient of both PVP and HPMC over that substrate, no matter which method was used for the calculation. On the

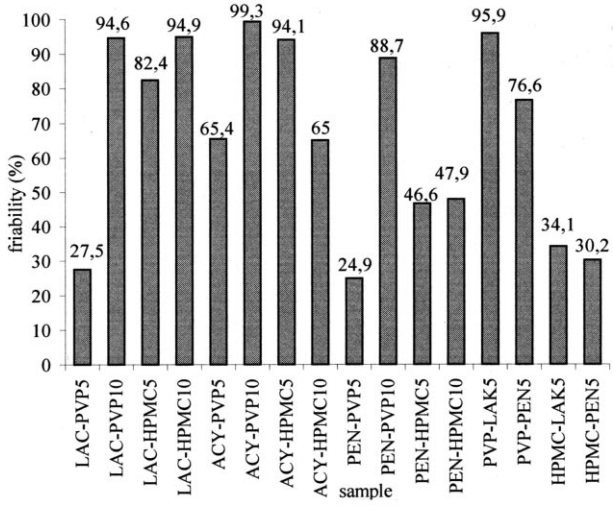

Fig. 2. Friability of the granules.

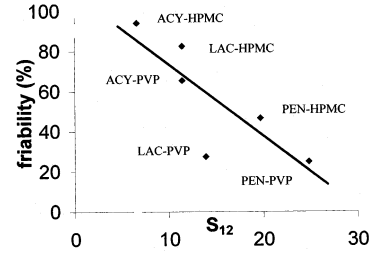

Fig. 5. Correlation of spreading coefficient over model substances with friability of the granules with 5% of binder (calculated according to Della Volpe).

contrary, the comparison of binder spreading coefficient values over the same substrate depends on the calculation method used (Tables 6 and 7). Friability results show that PVP is more efficient than HPMC when added in concentrations of 5% (Fig. 5). This result is in agreement with spreading coefficient values only when Della Volpe's method is used (Tables 6 and 7, and Figs. 3–5; spreading coefficient for PVP over the same substrate is greater than for HPMC). It seems that calculation of solid-surface free-energy parameters with electron donor and electron acceptor parameters of liquids that were modified by Della Volpe and Sibioni (1998) gives a better correlation with granule properties than any other method. The results of the two other methods used for spreading

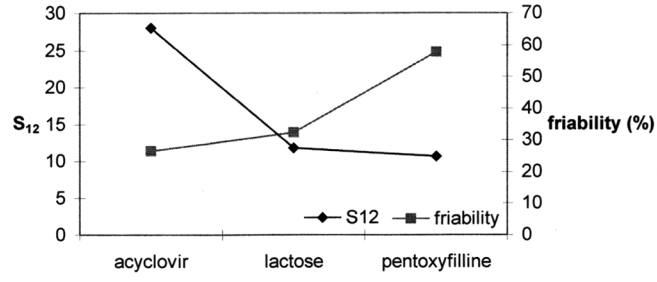

Fig. 3. Correlation of PVP spreading coefficient over the model substances (S_{12}) with friability of the granules with 5% of binder (calculated according to Della Volpe).

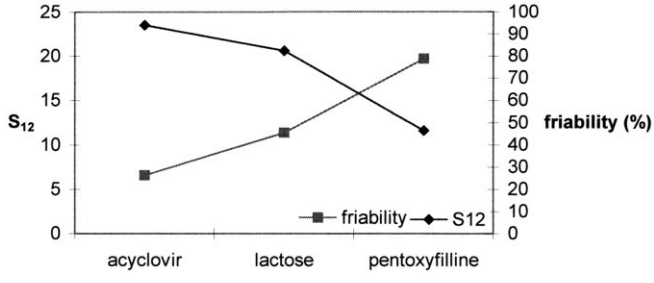

Fig. 4. Correlation of HPMC spreading coefficient over the model substances (S_{12}) with friability of the granules with 5% of binder (calculated according to Della Volpe).

coefficient calculation show very little difference and cannot be used to predict which binder should be more appropriate for granulation of a certain substrate (lactose, acyclovir and pentoxyfilline).

Friability of the granules depends on the work of cohesion of the binder and the substrate, and the work of adhesion between both components. Generally, for the binder to spread over the substrate, the work of cohesion of the binder must be lower than that of the substrate. In that case, granule friability depends on work of adhesion and binder work of cohesion.

Higher friability of the granules with HPMC (5%) than with PVP (5%) can be explained in terms of lower cohesion work of HPMC and lower work of adhesion (Table 8). The same conclusion can be reached irrespective of the method used for the calculation. In spite of the fact that the different methods used for surface energy determination gave different results, the relative comparison of the samples in this case leads to the same conclusions: comparison of adhesion work with cohesion work of the binder leads to the thesis that binder work of cohesion strongly influences the friability of the granules.

When the amount of binder added to the substrate is increased from 5 to 10%, the friability becomes significantly higher and the median granule size increases. This result leads to the conclusion that concentration exceeds the optimum and that the binder starts to spread over the granules in several layers. Total coverage of the lactose can be observed when comparing scanning electron microscopy (SEM) micrographs of the samples LAK-PVP5 and LAK-PVP10 (Fig. 6). Higher amounts of binder (i.e. 10%) result in an increased median granule size. This means that

Table 8
Work of cohesion of the binders and substrates, and work of adhesion between binder and substrate (mN/m)

	Wu			Good–van Oss			DellaVolpe		
	W_c	W_a(PVP)	W_a(HPMC)	W_c	W_a(PVP)	W_a(HPMC)	W_c	W_a(PVP)	W_a(HPMC)
PVP	100.8			88.6			89.0		
HPMC	91.4			76.8			83.2		
Lactose	138.8	113.0	104.5	114.4	100.7	89.1	110.6	103.1	94.6
Acyclovir	127.2	110.5	102.7	102.2	97.2	86.1	95.6	99.5	89.8
Pentoxyf.	154.2	117.5	108.4	112.4	107.7	89.9	127.0	114.0	102.9

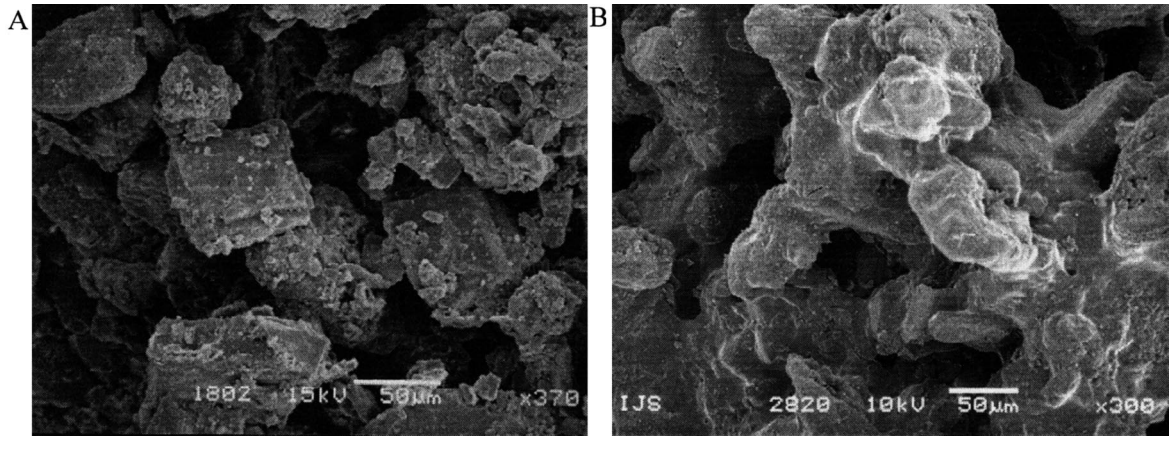

Fig. 6. SEM micrographs of LAK-PVP5 (A) and LAK-PVP10 (B).

Table 9
Liquid penetration velocity into powder samples (according to the Washburn method)

	HPMC (m^2/t) (g^2/s)	PVP (m^2/t) (g^2/s)
Hexane	$(209.69 \pm 15.54) \times 10^{-4}$	$(208.52 \pm 6.29) \times 10^{-4}$
Heptane	$(212.89 \pm 26.03) \times 10^{-4}$	$(191.72 \pm 15.32) \times 10^{-4}$
1-Octanol	$(19.61 \pm 0.05) \times 10^{-4}$	$(8.45 \pm 0.28) \times 10^{-4}$
1-Butanol	$(30.58 \pm 4.16) \times 10^{-4}$	$(0.05 \pm 0.02) \times 10^{-4}$

Table 10
True density of the granule components

Sample	True density (g/cm^3)
PVP	1.23
HPMC	1.32
Pentoxyfillin	1.36
Acyclovir	1.55
Lactose	1.55

the granules are composed of subgranules that are bonded mostly through cohesive interactions of the binder. Lower cohesion of the binder than adhesion between the binder and substrate, and cohesion in the substrate causes formation of more friable granules. The deviation in the case of acyclovir and HPMC granulate was observed as the amount of binder in the formulation was increased from 5 to 10%; it caused a decrease in granule friability. It is possible that optimum binder concentration is not yet reached at the 5% level, which can be in correlation with the smallest particle size of acyclovir and its anticipated highest specific surface. On the basis of these results, one can expect the parabolic dependence in the plot of friability versus concentration of a binder in the formulation. Additionally, the empirical finding that concentration of binder usually varies from 2 to 10% is in agreement with our results.

In the production of the inverse granules, the process was constructed by way of spraying the suspension of model substance (in GPCG1) on the binder powder. Granulates consisted of 95% PVP or HPMC and 5% lactose or pentoxyfilline (Table 2). These were produced to test the Rowe postulate, which states that when the spreading coefficient of a binder over the substrate is negative, more friable granulate should be formed. From Fig. 1, it can be seen that the particle diameter of PVP and HPMC increased significantly. When comparing friability results, one can see that samples PVP-LAK5 and PVP-PEN5 are much more friable than samples HMPC-LAK5 and HPMC-PEN5. According to the spreading coefficient results, it can be concluded that, in the production of these granulates, the binders PVP and HPMC spread over the substrate. Fluid bed granulation is a dynamic process where powder in the expansion chamber is wetted during granulation process. Difference in the friability of granulates containing PVP from granulates containing HPMC can be explained with the results of a Washburn penetration method. This was used for measuring the wetting kinetics. For the nonpolar liquid used for penetration measurements (hexane and heptane; Table 9), the penetration velocity is similar for both binders. Partially polar liquids 1-butanol and 1-octanol penetrate into HPMC much faster than into PVP. According to this result, it could be postulated that water (that failed to penetrate in Washburn method measurements) wets HPMC much faster than PVP during the granulation process, giving only HPMC enough time to spread over the lactose or pentoxifilline and form less friable granules.

It was expected that the true density of the granules could be a reflection of adhesion interactions between bonding agent and substrate. Results show that, in most cases, density did not change much in comparison with theoretical true density that was calculated for physical mixtures of the same composition as the produced granulate (Tables 10 and 11). In some cases, the decrease of true density of granules in comparison with that of a physical mixture is in good correlation with the observed friability of the granulates (LAK-PVP10, LAK-ACY10; Tables 8 and 11)

As already mentioned, the increase of the binder amount in the formulation leads to

Table 11
Theoretical true density of the physical mixtures, measured true density, bulk density and tap density of produced granulates

Sample label	Theoretical true density	Measured true density	Bulk density	Tapp density
LAK-PVP5	1.53	1.51	0.277	0.350
LAK-PVP10	1.53	1.43	0.260	0.337
LAK-HPMC5	1.53	1.56	0.240	0.330
LAK-HPMC10	1.53	1.56	0.191	0.252
ACI-PVP5	1.53	1.54	0.260	0.340
ACI-PVP10	1.52	1.45	0.209	0.274
ACI-HPMC5	1.54	1.55	0.240	0.330
ACI-HPMC10	1.53	1.58	0.211	0.282
PEN-PVP5	1.36	1.34	0.280	0.350
PEN-PVP10	1.36	1.35	0.232	0.276
PEN-HPMC5	1.36	1.38	0.270	0.340
PEN-HPMC10	1.36	1.38	0.195	0.243
PVP-LAK5	1.24	1.26	0.164	0.207
PVP-PEN5	1.24	1.23	0.207	0.243
HPMC-LAK5	1.33	1.50	0.059	0.098
HPMC-PEN5	1.32	1.44	0.069	0.103

formation of friable granules, which correlates with the bulk, and tap density results (Table 11). Increases of binder amount in the formulation causes a decrease in bulk and tap density; granulates become more voluminous. These results confirm that a certain amount of the binder in the granulate covers the substrate. This means that, at the beginning, strong bonds are present between the binder and substrate (high work of adhesion; Table 8), but further addition of the binder influences the formation of bigger agglomerates in which particles are connected with weaker binder cohesion interactions (low work of cohesion).

5. Conclusion

A very good correlation was achieved between the spreading coefficient of binder over the substrate and the friability of the granulates. It was also found that, in certain circumstances, the wetting kinetics might play an important role in the granulation process, especially in the fluid bed granulation. The results lead to the conclusion that not only are optimal process parameters needed for successful granulation, but also the surface free energy of the formulation ingredients plays an important role.

Acknowledgements

The authors greatly appreciate the substance donation of the pharmaceutical companies LEK d.d. (Ljubljana, Slovenia), KRKA d.d. (Novo mesto, Slovenia) and SYNTHAPHARM (Germany).

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