University of Szeged
Faculty of Pharmacy
Department of Pharmaceutical Technology
Head: Prof. Dr. Habil. Piroska Szabó-Révész Ph.D.

Doctoral dissertation

INFLUENCE OF THE SURFACE FREE ENERGY ON THE PARAMETERS OF PELLETS

By

Zsófia Tüske

Pharmacist

Supervisor:
Prof. Dr. Habil. Klára Pintye-Hódi Ph.D.

Szeged
2005

Publications

I. Bajdik J., ***Tüske Zs.***, Hódi K., Erős I.: A felületi jelenségek szerepe a szilárd anyagok feldolgozása során. I. rész. A jelenségek elméleti háttere Acta Pharm. Hung. 73 (2003) 80-85

II. ***Tüske Zs.***, Bajdik J., Hódi K., Erős I.: A felületi jelenségek szerepe a szilárd anyagok feldolgozása során. II. rész. A szilárd anyagok határfelületi jelenségeinek kísérleti vizsgálata. Acta Pharm. Hung. 73 (2003) 86-91

III. J. Bajdik, K. Pintye-Hódi, O. Planinšek, ***Zs. Tüske***, L. Tasic, G. Regdon jr., S. Srčič, I. Erős: Surface treatment of indomethacin agglomerates with eudragit. Drug Dev. Ind. Pharm. 30 (2004) 381-388

IV. Hódi K., ***Tüske Zs***., Bajdik J.: Szilárd gyógyszerformák előállításának fizikai kémiai alapjai. Acta Pharm. Hung. 74 (2004) 90-101

V. ***Zs. Tüske***, G. Regdon jr., I. Erős, S. Srčič, K. Pintye-Hódi: The role of the surface free energy in the selection of a suitable excipient in the course of a wet-granulation method. Powder Technol. 155 (2005) 139-144

Abstracts

I. ***Tüske Zsófia***: Diclofenac-Na tartalmú pelletek előállítása és vizsgálata. Tudományos Diákköri Konferencia, Szeged, 2001, február 15-17.

II. ***Tüske Zsófia***: Diclofenac-Na tartalmú pelletek előállítása és vizsgálata. XXV. Országos Tudományos Diákköri Konferencia, Pécs, 2001, április 4-7.

III. ***Tüske Zsófia***: A felületi energia szerepének tanulmányozása a pelletkészítés során. VI. Clauder Ottó Emlékverseny, Budapest, 2002. szeptember 26-28.

IV. Bajdik János, Hódi Klára, ***Tüske Zsófia***, Erős István: Felületi jelenségek szerepe a porok feldolgozásában. XIV. Országos Gyógyszertechnológiai Konferencia, Héviz, 2002. november 8-10.

V. Kása Péter, ***Tüske Zsófia***, Hódi Klára, Erős István: Összetétel és készítési paraméterek befolyása a pelletkészítésben. XIV. Országos Gyógyszertechnológiai Konferencia, Héviz, 2002. november 8-10.

VI. ***Tüske Zsófia***, Hódi Klára, Bajdik János, Erős István, Srčič Stane: Az adhézió és a felületi energia szerepe a szilárd gyógyszerformák formulálása során. XIV. Országos Gyógyszertechnológiai Konferencia, Héviz, 2002. november 8-10.

VII. ***Tüske Zsófia***, Erős István, Hódi Klára: A felületi szabadenergia szerepe centrifugál-granulátorban történő pelletelőállítás során. Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium 2003. Eger, 2003. szeptember 22-23. pp. 6.

VIII. ***Tüske Zsófia***, Erős István, Hódi Klára: A felületi szabadenergia szerepe nedves granulálással előállított pelletek formulálása során. Congressus Pharmaceuticus Hungaricus XII. Budapest, 2003. május 8-10. pp. 91.

IX. ***Zsófia Tüske***, István Erős, Klára Pintye-Hódi: The effect of the surface free energy on the production of pellets. International Congress for Particle Technology (PARTEC 2004), Nuremberg, Germany, 16-18.03.2004.

X. ***Tüske Zsófia***: Felületi szabadenergia meghatározó módszerek összehasonlítása. Gyógyszer az ezredfordulón V. Az európai csatlakozás küszöbén-Továbbképző konferencia, Sopron, 2004, március 25-27. pp. 5.

XI. ***Tüske Zsófia***: A felületi szabadenergia szerepe a megfelelő segédanyag kiválasztásában pelletelőállítás során PORANAL IX. Szemcseméret-analitikai, Környezetvédelmi és Portechnológiai Szimpózium, Balatonfüred, 2004. szeptember 5-7. pp. 22-23.

XII. ***Zsófia Tüske***, István Erős, Klára Pintye-Hódi: Investigation of the surface free energy of metronidazole - corn starch mixtures and of pellets made from the mixtures. 6th Central

European Symposium on Pharmaceutical Technology and Biotechnology, Siófok, Hungary, 25-27. 05. 2005.

Abstract in Eur. J. Pharm. Sci., 25 Suppl. 1, S1-S226 (2005) P-92

CONTENTS

1. Introduction

Solid dosage forms (pellets, tablets or capsules) are the most frequently used pharmaceutical dosage forms in therapy. They play an important role in the pharmaceutical industry. In the course of the production of solid dosage forms, numerous problems have to be taken into consideration. The elimination of unfavourable phenomena and the solution of problems are highlighted fields in pharmaceutical technology. The factors influencing the granule/pellet parameters, which pellets may be separate dosage forms or intermediates in tabletting and in capsule filling, and the optimization of these factors are still topics of research. There are many influential factors. The roles of several factors are well known, but the effects of some are not completely solved.

In the course of pelletization, a knowledge of the properties of the active agents and the excipients is very important. The wettability and the surface free energy of solids are momentous physical-chemical parameters in the design of pharmaceutical formulations. Their determination is possible in several ways. This type of information can help in the selection of the components if the interfacial interactions and compatibility of the formulation components are known.

A knowledge of surface free energy is of great significance for an understanding of the interactions between the particles of powders and powder mixtures [1] and the accessories of the equipment [2, 3] in the course of various technological procedures (powder mixing [4], granulating, pelletizing [5-7], capsule filling [8-10], tabletting [11] and film coating [12]. In the course of pellet making, the aim is to produce a product with appropriate mechanical properties, which is proof against the mechanical effects experienced during the further processing (capsule filling or film coating).

2. Aims

Pellets containing metronidazole were produced in a centrifugal granulator from the model active agent. The typically large metronidazole crystals were not ground or milled in order to avoid changes in the surface and the physico-chemical properties of the particles. The part of the surface free energy in wet-granulation has been discussed in various papers. Those investigations were made with binary systems (one powder component and binder) [5-7]. The publications tended to select the suitable binder for a model excipient or active agent.

References to the author's own articles are made with bold numbers.

During the building-up of the pellets, the spreading coefficient, the work of adhesion and cohesion, the particle size and the binder solution applied are all determining factors. For a binary system (one powder and binder), connections can be found between the spreading coefficient and the pellet parameters (primarily the friability). For systems containing many components, the selection of a suitable excipient(s) to produce a product from an active agent is a complex task. There are several factors, which must be considered.

The aims of the present work were as follows:

To review the role of surface free energy as an important physical-chemical parameter during the development of solid dosage forms, especially in the field of wet-granulation.

The aim was to investigate the role of the surface free energy of one- and two-component powder compositions in the pellet production.

The first aim of the study was to investigate the role of surface free energy in the formation of pellets from one- and two-component powder compositions and to choose a suitable excipient (active agent - excipient - binder systems). The surface free energies of the *powder components* were determined.

The second aim was to investigate whether the surface free energy of a powder mixture depends on the proportions of the components, and how the forces of cohesion and adhesion between the particles affect their interactions as functions of the proportions of the components. The surface properties of the *powder mixtures* were investigated.

The third aim was to study the role of surface free energy in the formation of pellets from two-component powder compositions containing different amounts of a poorly water-soluble model drug and an excipient, and to look for connections between the properties of the mixtures and the pellet properties.

3. Literature survey

3.1. Pellets

Pellets are nearly spherical agglomerates with flat surface, low porosity and good flowability. Pelletization is a procedure of agglomeration in which small particles are transformed into larger spherical units, usually 0.5-3.0 mm in diameter. The particle size, however, can vary with the production technology and time [13-17].

In their use, pellets can be:

- Separate dosage forms;

- Intermediates in tabletting, with the aim of improving the flowability of materials which cannot be tabletted directly. The pellets produced involve larger and more flowable particles with lower specific surface and adhesion than those of the particles of the original powder mixture;
- Capsule fillings due to their morphology, good flowability and mechanical property;
- Intermediates, which are appropriate for coating due to their spherical shape, flat surface and mechanical stability.

3.1.1. Historical survey

The enlargement of particulate solids by agglomeration is many thousands of years old. Such aggregates have been applied in therapy [18]. The granulate as a separate dosage form appeared in the early 20th century in France [19]. A serious breakthrough was achieved in 1949 by the researchers of Smith, Kline and French (SKF). The production of preparations with an extended effect became possible by using sugar particles, pellets of which were filled in gelatine capsules. This technology was a build-up process. A patent for spray-freezing was granted in 1964. With this method, pellets with extended release were processed. Pellet production was revolutionized by extrusion-spheronization technology, which was developed in the 1960s in Japan. Through use of this technology, large quantities of product could be produced during a short working period. Currently, different build-up technologies and the extrusion-spheronization technology are the most up-to-date [20].

3.1.2. Possibilities of pellet production

The pellets used in the pharmaceutical industry according to the producing technology may be build-up pellets, produced by extrusion-spheronization, pelletizing by kneading or spray-freezing technologies.

During the production of **build-up pellets**, the powder mixture is kept in motion while the granulating fluid (binder solution) is being sprayed uniformly on the surface of the particles. The particles will aggregate and the fluid bridges transformed into firm binding bridges by the concurrent drying. Types of apparatus producing pellets by this technology include the dragée pan, rotating drum, fluidizing apparatus [21-24] and centrifugal granulator.

Centrifugal granulator: The upper part of the equipment is a cylindrical body, and the lower part is a flat plate. The edge of the plate forms an arch and in the middle a conical rise can be seen, where the centrifugal force is low and hence the powder mixture never accumulates on the middle. The lower part goes round. Between the upper and lower parts is a slit, through which the slit air is flowing in. The formation of the spherical shape is due to the

effect of the centrifugal, gravitational and fluidizational forces. The drying through the slit air is not always sufficient. Secondary drying may be necessary in other equipment or in the open air [25-27].

Extrusion and spheronization is a compound process. In the first step, the powder mixture and the granulating fluid are kneaded into a wet mass, which is then passed through a perforated plate containing holes of appropriate size. The oblong (often cylindrical) plastic agglomerates are the extrudates. In the second step, the extrudates are spheronized/rounded in a spheronizer. Products with high active ingredient content can be achieved in a short working period via this technology [28-34].

Pelletizing by kneading: High-shear wet-granulation is a process that involves the intensive mixing of powders and fluid, which results in the formation of granules. Granule growth in high-shear wet-granulation is a dynamic process in which granules are continuously forming and breaking down. The granule size achieved with a given set of experimental conditions depends on the relative rates of granule formation and breakdown. Granule growth in a high-shear mixer proceeds initially by a nucleation mechanism. Liquid droplets are broken up and dispersed by the shear forces in the granulator and then proceed to wet the primary particle surface [35-41].

Pelletization with drop formation can be performed by technologies based on dropping or spraying of the melt [42, 43]. The active ingredient is dissolved or suspended in the melt of auxiliary material (fats, fatty acids, fatty alcohols, waxes, polyethylene-glycols, triglycerides or mixtures of these) [29]. In spray-freezing, the melt of the material to be grained is sprayed. The spray drops quickly form isometric solid particles. A new and modern method in the field of pharmaceutical technology is the melt solidification technique from drops [44, 45].

Other technologies include vacuum-granulation [46], dry-granulation [47], and use of a centrifugal-fluid-rotoprocessor [20].

3.2. Wettability

The wetting phenomenon can be explained by the interaction between interfaces. The behaviour of the liquid drop is determined by the interfacial tensions arising among the three interfaces, and according to the Young equation equilibrium arises when the vector sum of the surface forces is zero [48-50]. The model of the wetting is the contact angle, which is an interfacial physical phenomenon [51]. The thermodynamics of the contact angle is described by the Young equation [52]:

$$\cos\theta = \frac{\gamma_{SV} - \gamma_{SL}}{\gamma_{LV}} \quad (1)$$

where: γ_{SV} = interfacial tension between solid surface and vapour, γ_{SL} = interfacial tension between solid surface and liquid, and γ_{LV} = interfacial tension between liquid and vapour (*Figure 1.*).

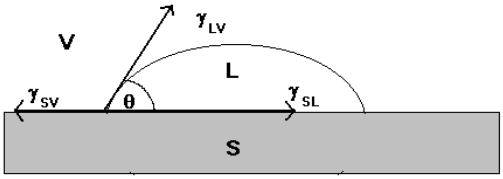


Fig. 1. Contact angle (θ) between solid surface and liquid

Three subtypes of wetting can be distinguished:

- A finite contact angle forms between the solid surface and the liquid (contact wettability).
- The liquid fully spreads on the solid surface and forms a continuous wetting layer (film wettability).
- The solid is fully immersed into the liquid (immersional wettability).

When a liquid fully wets a solid, the contact angle is zero. When a solid is not wetted by a liquid, the contact angle is ≈ 180°. In practice, solids with a contact angle < 90° can be regarded as well wetted. Solids with an angle > 90° are poorly wetted [53, 54]. Various techniques are applied to determine the contact angle (the sessile-drop method, an optical method; the powder contact angle method, based on the penetration; and the Wilhelmy plate method, based on force measurement) [55].

3.3. Determination of surface free energy

The surface free energy of solids can be derived from the contact angle which the different liquids form on the surface of the solid compacts. The theory of calculating the surface free energy of solids is based on the different wetting properties of the different surfaces with the same liquid. On the other hand, the contact angles of different liquids on the same surface are different.

The surface free energy is the surface free energy change when the surface area of a medium is increased by unit area. For solids, the surface free energy is commonly denoted by γ_s and is given in units of energy per unit area, mJ/m^2 (or mN/m).

For many solid materials present in forms with smooth, flat surfaces, the contact angle and the surface free energy can be determined relatively simply. For pharmaceutical solids, which are usually powders, the situation is more difficult, due to the particle shape, size and surface of these materials [56]. Accordingly, various techniques are applied to determine the wettability and surface free energy of powders [57-65]. The method of assessing the surface free energy indirectly from wettability measurements is widely used [66, 67]. The measurements are usually carried out on the surface of the compacts made from the solid powders.

In the method of Wu [68, 69], the surface free energy is taken as the sum of dispersive (d) and polar (p) components ($\gamma_s = \gamma_s^d + \gamma_s^p$) [70, 71]. The surface free energies of solid materials can be determined by means of contact angle measurements on two liquids with known polarities. They can be assessed by solving two equations with two unknowns:

$$(1+\cos\Theta)\gamma_l = \frac{4(\gamma_s^d \gamma_l^d)}{\gamma_s^d + \gamma_l^d} + \frac{4(\gamma_s^p \gamma_l^p)}{\gamma_s^p + \gamma_l^p} \qquad (2)$$

where Θ is the contact angle, γ_s is the solid surface free energy and γ_l is the liquid surface tension **[72]**.

On finding that all systems cannot be described by means of Wu's method, Good and van Oss upgraded it. The surface free energy is divided into polar (AB) and nonpolar (Lifshitz–van der Waals (LW)) parts, and the surface free energy is the sum of these parts **[73]**. The polar part (AB) is further divided into electron donor (base γ^-) and electron acceptor (acid γ^+) parameters. The acid–base (AB) component of the surface free energy is estimated from Eq. (3) and the surface free energy from Eq. (4). The contact angles of three liquids with known surface tension components must be used to determine the three unknown components of the solid surface free energy (γ_s^{LW}, γ_s^+ and γ_s^-). Thus, three equations of Eq. (4) type must be solved simultaneously [74, 75]:

$$\gamma_i^{AB} = 2\sqrt{\gamma_i^+ \gamma_i^-} \qquad (3)$$

$$(1+\cos\theta)\gamma_l^{TOT} = 2\left(\sqrt{\gamma_s^{LW}\gamma_l^{LW}} + \sqrt{\gamma_s^+\gamma_l^-} + \sqrt{\gamma_s^-\gamma_l^+}\right) \qquad (4)$$

The surface free energy of solid materials can also be determined by means of inverse phase gas chromatography (IGC). Although IGC was introduced in different fields long ago, it has been applied to pharmaceutical systems only in the last 10 years [76-84]. The advantage of this method is that the studied particles and their surface do not change during the

preparation of the sample. The solid to be studied is packed into a column and a known gas is passed over its surface. By injecting a series of alkanes with known surface free energy (in this case $\gamma_l^d = \gamma_l$) into the gas flow, the dispersion component, γ_s^d, of the solid surface free energy can be determined. The retention volume may be calculated from Eq. (5) [85], and γ_s^d from Eq. (6) [86].

$$V_n = JF(t_r - t_0) \tag{5}$$

$$RT \ln V_n = 2N\sqrt{\gamma_s^d}\, a \sqrt{\gamma_l^d} + K \tag{6}$$

where F is the carrier gas flow; J is the James and Martin compressibility correction factor [87], due to pressure differences; t_r is the retention time of the probe; t_0 is the retention time of the non-interacting standard (methane); a is the molecular area of the adsorbed molecule; R is the gas constant; T is the absolute temperature; K is the intercept; and N is Avogadro's number.

The electron donor or acceptor character of the solids can be determined by using polar probe liquids, which gives information about the polar character of the solids.

3.4. Parameters calculated from surface free energy

To characterize complex systems, the surface free energy alone does not give sufficient information. Further parameters can be calculated from the surface free energy. The distribution in a two-component system can be characterized with the spreading coefficient. If the surface free energies of the solid materials are known, the spreading coefficient (S) may be computed and the interactions between the two materials may be predicted [4]. The spreading coefficient is calculated as the difference between the adhesion work (W_a) and the cohesion work (W_c). The two materials which interact can be two powders, a powder and a liquid (for example, a powder and a granulating fluid) or any material and the equipment. The spreading coefficient of a material over the surface of another material (S_{12}) and that of the second material over the first (S_{21}) can be determined according to Eqs (7) and (8) [88]:

$$S_{12} = 4\left[\frac{\gamma_1^d \gamma_2^d}{\gamma_1^d + \gamma_2^d} + \frac{\gamma_1^p \gamma_2^p}{\gamma_1^p + \gamma_2^p} - \frac{\gamma_1}{2}\right] \tag{7}$$

$$S_{21} = 4\left[\frac{\gamma_1^d \gamma_2^d}{\gamma_1^d + \gamma_2^d} + \frac{\gamma_1^p \gamma_2^p}{\gamma_1^p + \gamma_2^p} - \frac{\gamma_2}{2}\right] \tag{8}$$

where γ^d is the dispersion solid surface free energy, γ^p is the polar component of the surface free energy and γ is the total surface free energy.

The work of adhesion and the surface free energy may be calculated from each other [89, 90]. If work of cohesion is performed, two new surfaces of unit area are formed from an originally homogeneous body. The work input must compensate for the surface free energy of the new surfaces. The work of cohesion ($\Delta\gamma_c$ [mJ/m^2]) and surface free energy (γ_s) are normalized for unit area; Eq. (4) can be used:

$$W_c = 2\gamma_s \tag{9}$$

According to Dupré [91], the work of adhesion ($\Delta\gamma_a$) describes the work necessary to separate two phases so that two new surfaces of unit area are formed, but this time from different materials. The work input must compensate for the surface free energies (γ_{s1} and γ_{s2}) of the new surfaces. However, through the separation of the solid-solid interface, the work is lower by the interfacial energy ($\gamma_{s1,s2}$):

$$W_a = \gamma_{s1} + \gamma_{s2} - \gamma_{s1,s2} \tag{10}$$

The work of adhesion (W_a) is equal numerically to the energy that arises when two surfaces come into contact [92-94]:

$$W_a = 4\left[\frac{\gamma_1^d \gamma_2^d}{\gamma_1^d + \gamma_2^d} + \frac{\gamma_1^p \gamma_2^p}{\gamma_1^p + \gamma_2^p}\right] \tag{11}$$

3.5. Application of surface free energy

A knowledge of the surface free energy is of great significance for an understanding of the interactions between the particles of powders and powder mixtures [1] and the accessories of the equipment [2] in the course of various technological procedures. For this reason, it is important during powder mixing and tabletting. The surface free energy data of pharmaceutical powders can be utilized in the formulation of wet-granulation processes in order to select a suitable binding agent and to predict granule/pellet properties via the binder - substrate S values [88, 95-99]. This type of information can also help in the selection of the most suitable coating liquid during film coating [12, **100**], and it can help in the choice of the cooling plate for melt technology [45]. During tabletting and capsule filling, the knowledge of the interactions between the particles and between the particles and the surface of the equipments can be used. A knowledge of the interactions among the particles is also impotant during the development of dry powder inhalers [101].

During the design of a solid pharmaceutical formulation from an active agent, it is necessary to know the surface properties of the materials applied and the interactions between them **[102]**. The surface free energy can help to solve different technological problems and also to give additional information about the materials applied during the development phase. This information can help to eliminate the effect of several unfavourable factors.

4. Materials and methods

4.1. Materials

Metronidazole (Ph. Eur. 4th) is a white to yellowish-white crystalline powder. It is poorly soluble in water. It is a drug frequently used in the treatment of various anaerobic infections. It is well absorbed following oral administration. The drug is a useful prophylactic in obstetrical and gynaecological interventions, colorectal surgery and appendectomy [103-106]. Its single oral dose is generally 250 mg and the tablets have a high active agent content [107]. The drug and its actions (doses) have been discussed in various papers [108-115].

Hydroxypropyl cellulose (Klucel LF) (Hercules Inc., USA), a partially substituted poly(hydroxypropyl)ether of cellulose. Hydroxypropyl cellulose is a white to slightly yellow, odourless, tasteless powder. It is freely soluble in water below 38 ºC, forming a smooth, clear, colloidal solution [116]. It is used as a binder during wet-granulation and as a binder, film coating and extended-release matrix former in tableting [117-119]. It displays surface activity and can promote the dissolution of the drug from tablets [120, 121].

Corn starch (Ph. Eur. 4th) consists of amylose and amylopectin, two polysaccharides based on α-glucose. Starch occurs as an odourless, tasteless, fine white powder, comprising very small spherical granules whose size and shape are characteristic. Starch is used as an excipient primarily in oral solid-dosage formulations, where it is utilized as a binder, diluent and disintegrant [122-126]. It does not dissolve in water, but swells [116].

Microcrystalline cellulose (Vivapur 101) (Rettenmaier & Söhne GmbH & Co., Rosenberg, Germany) is a purified, partially depolymerized cellulose that occurs as a white, odourless, tasteless, crystalline powder composed of porous particles. It is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations, where it is applied in both wet-granulation and direct conpression processes. In addition to its use as a binder/diluent, it also has some lubricant [127] and disintegrant properties that make it useful in tableting.

α-Lactose monohydrate (Ph. Eur. 4th) occurs as white to off-white crystalline particles or powder. It is odourless and slightly sweet-tasting. It is a disaccharide, consisting of glucose and galactose. It is widely used as a filler or diluent in solid-dosage forms.

The liquids used for contact angle measurements were **glycerol** (Riedel-de Haën AG, Germany) (γ^d = 32.0 mN/m, γ^p = 31.7 mN/m) and **diiodomethane** (Sigma, Germany) (γ^d = 50.8 mN/m, γ^p = 0 mN/m).

4.2. Methods

4.2.1. Contact angle measurements

In the first part of the investigations (see section 5.1.) the contact angles were measured with the Wilhelmy-plate method, and in the second part (section 5.2.) with the sessile-drop method. The contact angle was determined in both cases with glycerol and diiodomethane, as such measurements were impossible with water because of the resulting disintegration of the compacts containing corn starch. The surface free energy was calculated according to the method of Wu, using Eq. (2). Differences were found in the contact angle and surface free energy data of the same material when the two different methods were used. A characteristic tendency can be observed in the data, in spite of the application of the two different measuring methods. The same method was used in the various procedures.

4.2.1.1. Wilhelmy contact angles

Compacts of the powders (200 mg) were made in a highly polished stainless steel punch and die assembly (2.5×10 mm) in a Specac hydraulic press (England) with a 10 s dwell time and at a pressure of 2×10^8 Pa. The perimeter of the plate samples was measured accurately with a micrometer. The contact angle of the solids was determined by means of the Wilhelmy plate technique, using a Krüss Tensiometer K12 (Germany). Temperature was controlled at 20 ± 0.5 °C, with water flowing from a circulator (Haake, Germany). The test liquid (glycerol or diiodomethane) was placed in a special glass dish and raised at a speed of 1.2 mm/min by means of a motorized platform to contact the powder plate. From the force measurements, the contact angle was obtained with the Krüss tensiometer software [55, 128]. Five plates of the same powder were used for measurements with each liquid. The experimental technique is described elsewhere [129, 130].

4.2.1.2. Dynamic sessile drop contact angles

Compacts of the powders (150 mg) were made with a highly polished stainless steel punch (13 mm in diameter) in a Specac hydraulic press (Specac, England) with a 10 s dwell time and at a pressure of 2×10^8 Pa. The contact angle of the solids was determined by means of the sessile drop technique (OCA 20 Dataphysics Instruments GmbH, Fielderstadt, Germany), using a charging pipette (Hamilton Microliter Syringe). Photos were taken with a video camera every second up to 10 s from the coming into contact of the drop with the compact. The contact angles were calculated from the contours of the drop [131]. The values at 1 s were used for the calculation of surface energy.

4.2.2. Calculation of surface free energy

The surface free energies of the materials were calculated according to the method of Wu, where the surface free energy is taken as the sum of dispersive and polar components. The polarity percentage was also calculated: $\left(\gamma_s^p / \gamma_s\right)\times100$.

4.2.3. Production of pellets

The particle size distribution and average size of the powders were measured with a Laborlux S light microscope and a Quantimet 500 MC (Q 500 MC) image analyser system (Leica Cambridge Ltd., Cambridge, UK). 500 particles were analysed. Particle size distributions for each powder were obtained through a frequency by number analysis [132]. The average particle sizes of the powders used in the centrifugal granulator are shown in *Table 1*.

Pellets containing metronidazole were prepared from a powder mixture of the drug and pharmaceutical additives using a centrifugal granulator (Freund CF-360, Japan). Powder mixing was performed with a Turbula mixer (Willy A. Bachofen Maschinenfabrik, Basel, Switzerland) (50 rpm for 10 min). The binder solution used was in every case a 10% aqueous solution of Klucel LF. The produced pellets were dried at room temperature (23 ± 2 °C) for 48 hours.

Table 1.

Particle sizes of powders used in the centrifugal granulator

	Length (μm)	Breadth (μm)
Metronidazole	193.67 (± 98.32)	103.70 (± 48.26)

Vivapur 101	71.05 (± 43.14)	33.85 (± 19.86)
Corn starch	12.80 (± 3.06)	10.76 (± 2.52)
α-Lactose monohydrate	9.42 (± 7.08)	6.19 (± 4.68)

Pelletization was performed with the following parameters:

Rotor speed	200-240 rpm, raised in two steps (at 15 min to 220 rpm, and at 30 min to 240 rpm)
Duration of process	40 min
Inlet air temperature	50 °C
Outlet air temperature	27-30 °C
Flow rate of binder solution	10 ml/min
Slit air flow rate	130 l/min
Spraying air flow rate	13 l/min
Atomizing air pressure	4 kg/cm^2
Nozzle diameter	0.5 mm

4.3. Test methods

Pellets were fractionated on a vibration sieve shaker (Retsch GmbH & Co., Haan, Germany) for 2 min. Size fractions < 315, 315 - 630, 630 - 800, 800 - 1000 and > 1000 μm were collected. The investigations were performed with the size fraction 800 - 1000 μm. The size fraction 800 - 1000 μm accounts for 40-50% of certain pellets.

4.3.1. Morphological study

The powder mixtures and the textures of the pellets were investigated with a scanning electron microscope (SEM) (Hitachi 2400 S, Hitachi Scientific Instruments Ltd., Tokyo, Japan). A polaron sputter coating apparatus (Polaron Equipment Ltd., Greenhill, UK) was applied to create electric conductivity on the surface of the samples. The air pressure was 1.3-13.0 mPa [133, 134].

4.3.2. Friability

The friability was characterized by placing 5.0 g of the pellets in a 122 ml bottle, together with 12 g of stainless steel balls 8 mm in diameter. The bottle was then placed in a rotating shaker mixer (Turbula, Willy A. Bachofen Maschinenfabrik, Basel, Switzerland)

(50 rpm for 2 min). The abraded samples were sieved on a 400 μm sieve. The amount retained on the sieve was weighed and the friability percentage was calculated [(weight passing through the sieve/total weight) × 100]. The measurements were made in triplicate.

4.3.3. Process of pellet deformation

The breaking strength and the deformation process were studied with a modified breaking hardness tester (developed in the department). The process of breaking induced by the vertical downward pressure force was observed and the force needed to break the pellet and the deformation process was measured.

4.3.4. Bulk and tapped densities

An appropriate amount of the sample was gently added up to the 250 ml mark in a 250 ml tared graduated cylinder. The volume was then read directly from the cylinder and used to calculate the bulk density according to the relationship: mass/volume. For the tapped density, the cylinder was tapped 200 times, using a STAV 2003 Stampfvolumeter (Engelsmann A.G., Luwigshafen, Germany). The volume of the sample was then read off and used in the calculation. The results were calculated from 3 parallel measurements.

4.3.5. Porosity

The porosity of a sample was determined via the equation

$$\varepsilon = 1 - \frac{\rho_{\text{tap}}}{\rho_{\text{p}}} * 100 \qquad (12)$$

where ε, ρ_{tap} and ρ_p are the porosity, tapped density and pycnometric density, respectively [135]. A Quantachrome SPY-2 stereopycnometer (Quantachrome Corp., Syosset, New York, USA) was used to determine the pycnometric volumes of the samples. The pycnometric density was calculated from the mass and the pycnometric volume. Results are averages of three replicate determinations.

4.3.6. Cohesiveness

The compactibility were tested with a STAV 2003 Stampvolumeter (J. Engelsmann A.G. Apparatebau, Luwigshafen, Germany). Tapping tests were performed with 0-300 taps at 10-tap intervals. The Kawakita equation was applied to the data obtained from the tapping test, using the formula

$$\frac{\text{N}}{\text{C}} = \frac{\text{N}}{\text{a}} + \frac{1}{\text{ab}} \qquad (13)$$

where N is the tapping number, C is the degree of volume reduction, 1/a is a constant related to the volume reduction, called the compactibility, and 1/b is another constant, related to cohesion and called the cohesiveness [136, 137].

4.4. Statistical evaluation

The mathematical evaluation was carried out with the SPSS for Windows 9.0 package. The two-sample T-test was applied for the comparison of two groups of results. The one-way ANOVA test was performed for comparison of several groups of results. Regression analysis was applied for demonstration of a correlation between two variables. The confidence limit was in every case 95%. Accordingly, the difference was significant if $p < 0.05$.

5. Results and discussion

5.1. Role of surface free energy in selection of a suitable excipient

The role of the surface free energy in the selection of a suitable excipient was investigated through studies on pellet samples containing different fillers [138]. The first sample consisted only of metronidazole and no excipient. The other pellet samples consisted of the active agent and one of the selected excipients. The compositions of the powder mixtures from which the pellets were prepared are shown in *Table 2*. The powder mixtures contained 25% excipient. The excipients applied are widely used auxiliaries in the formulation of solid dosage forms. The binder solution used was in every case 400 g 10% aqueous solution of Klucel LF.

Table 2.

Compositions of powder mixtures

	Sample 1	Sample 2	Sample 3	Sample 4
Metronidazole	1000 g	750 g	750 g	750 g
Vivapur 101	-	250 g	-	-
Corn starch	-	-	250 g	-
α-Lactose monohydrate	-	-	-	250 g

The contact angles of the materials were measured in glycerol and diiodomethane by the Wilhelmy plate technique. Through the use of a glycerol-diiodomethane liquid combination, the surface free energy could be determined according to the method of Wu. The results used for the calculations of spreading coefficients are listed in *Table 3.*

Table 3.

Contact angles (θ) and surface free energies (γ) of materials used

	Contact angle (°)		Surface free energy (mN/m)			
	glycerol	diiodomethane	γ_s	γ_s^d	γ_s^p	Polarity (%)
Metronidazole	46.2 (± 0.1)	39.3 (± 0.3)	50.9	40.5	10.4	20.4
Vivapur 101	25.5 (± 0.3)	38.5 (± 0.1)	59.0	40.9	18.1	30.7
Corn starch	36.8 (± 0.6)	36.3 (± 0.2)	55.2	41.8	13.4	24.3
α-Lactose monohydrate	31.5 (± 0.1)	58.7 (± 0.4)	54.7	31.1	23.6	43.1
*Klucel LF**	*82.3 (±0.2)*	*63.1 (±0.3)*	*30.9*	*29.0*	*1.9*	*6.1*

**Klucel LF data were applied to calculate the S results.*

It can be seen that the surface free energy of Klucel LF is the lowest. The surface free energies of the materials (model drug, excipients and binding agent) were used to calculate the spreading coefficients (S_{12} and S_{21}) and the adhesion and cohesion work. These results can account for the properties of the pellets produced. When the spreading coefficient of a binder over the substrate (S_{12}) is positive, the formation of dense, non-friable pellets can be expected. A positive S with a high absolute value correlates well with the pellet friability for binary systems (substrate and binder systems) [97]. When the spreading coefficient S_{12} is negative and S_{21} is positive, the substrate adheres to the binder at isolated points. In this second case, the binder solution does not form a film around the powder particles, which leads to the pellets having a more porous, loose texture [1, 54, 139].

It can be seen in *Table 4.* that the spreading coefficient of Klucel LF (1) over the substrate (2) (S_{12}) is positive in every case, while that of the substrate over the binder (S_{21}) is negative.

Table 4.

Spreading coefficients of Klucel LF over substrates (S_{12}), and of drug over Klucel LF (S_{21}) (mN/m)

Substrates (2)	S_{12} (Klucel LF (1))	S_{21} (Klucel LF (1))
Metronidazole	12.2	-28.0
Vivapur 101	12.9	-43.4
Corn starch	13.3	-35.5
α-Lactose monohydrate	5.2	-42.6

The lowest spreading coefficient value (S_{12}) was observed for α-lactose monohydrate. From the results for the other substrates (metronidazole, Vivapur 101 and corn starch), therefore, it is to be expected that Samples 1, 2 and 3 will give non-friable, poorly porous pellets. In contrast, in the case of Sample 4, a more friable, porous product is expected.

The results are partly in accordance with the spreading coefficient data. The friability of Sample 1 is higher than expected (24%) (*Table 5.*).

The lowest friabilities of Sample 2 and Sample 3 are connected with the higher spreading coefficients of Klucel LF over the powders used in these compounds. The friability of Sample 4 meets expectations. However, the S values alone do not provide a sufficient explanation of the measured parameters for the produced pellets, e.g. Sample 1 (containing only metronidazole) has a high friability, in contrast with the prediction.

The texture and porosity of the pellets, and hence their friability, do not depend only on the spreading coeffficient. The friability of the pellets is influenced by the adhesion and cohesion work. In general, for the binder to spread over the substrate, the work of cohesion of the binder must be lower than the work of cohesion of the substrate. In that case, the friability of the pellets depends on the work of adhesion and the work of cohesion of the binder. Comparison of the work of cohesion of the binder with the work of adhesion indicates that the work of cohesion has a strong effect on the pellet friability.

Table 5.

Parameters of metronidazole and pellets

	Friability	Bulk density	Tapped density	Porosity

	(%)	(g/cm^3)	(g/cm^3)	(%)
Metronidazole	-	0.64 (± 0.00)	0.75 (± 0.00)	47.71 (± 0.10)
Sample 1	24.4 (± 0.2)	0.54 (± 0.00)	0.57 (± 0.00)	60.36 (± 0.12)
Sample 2	13.5 (± 1.4)	0.52 (± 0.01)	0.55 (± 0.00)	62.40 (± 0.02)
Sample 3	11.5 (± 1.7)	0.62 (± 0.00)	0.66 (± 0.00)	54.48 (± 0.07)
Sample 4	19.9 (± 2.0)	0.63 (± 0.01)	0.67 (± 0.01)	54.51 (± 0.03)

When the amount of binder added to the substrate is increased, the friability becomes higher. When the concentration (binder) exceeds the optimum, the binder solution begins to spread over the pellets in several layers. The granules/pellets are aggregates of subgranules that are bonded mostly through cohesive interactions of the binder. In this case, the work of cohesion of the binder is lower than the adhesion work (between the binder and the substrate) and the work of cohesion of the substrate produces granules with higher friability [1]. Accordingly, a certain amount of the binder in the pellet compound can cover the substrate.

Our results show (*Table 6.*) that the work of cohesion of the binder is lower than the work of cohesion of the substrates and this favours the binder spreading over the substrate. The adhesion work between the binder and substrates is in every case higher than the work of cohesion of Klucel LF and this helps the binder to spread over the substrate too. However, differences can be seen between these results. The work of adhesion between α-lactose monohydrate and Klucel LF is lower than the work of adhesion of other substrate - binders. This is to be seen from the parameters of Sample 4. Samples 2-4 are compound systems. Accordingly, the work of adhesion between the substrates (inside the pellet powder mixture) was calculated and compared with the work of cohesion of the substrates and binder. The work of adhesion for the excipient - metronidazole composition is higher than the work of cohesion for Klucel LF. The binder spreads over the substrate in this case too.

Table 6.

Work of cohesion and adhesion (mN/m)

	W_c	W_a (Klu.LF)	W_a (Metr)
Metronidazole	101.9	73.9	-
Vivapur 101	117.9	74.5	107.8
Corn starch	110.5	75.0	105.8
α-Lactose monohydrate	109.5	66.9	99.3
Klucel LF	61.7	-	-

W_c: work of cohesion of binders and substrates

W_a (Klu.LF): work of adhesion between binder and substrates

W_a (Metr): work of adhesion between metronidazole and the other substrates

For Sample 1 (containing only metronidazole), the high friability can be explained by the relatively large particle size, and hence by the relatively smaller surface. The same amount of binder solution spreads over the metronidazole particles in several layers and is partly enclosed among the crystals (*Figures 2. and 3.*). The granules formed in this case have a loose, porous structure. The binding force is not strong, because the work of cohesion of the binder is determining and this work is low. The higher friability can be explained as before. The bulk and tapped densities of this product are low, and the granules are voluminous.

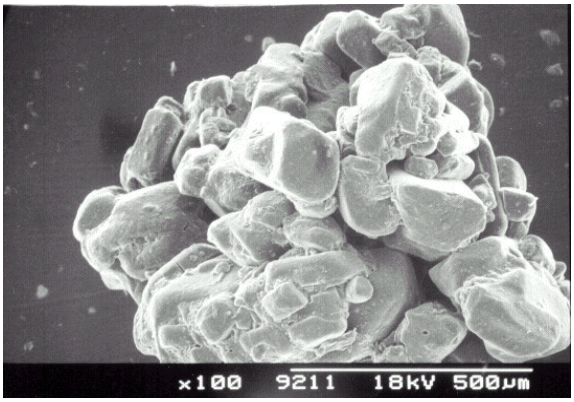


Fig. 2. SEM micrograph of Sample 1 (100×)

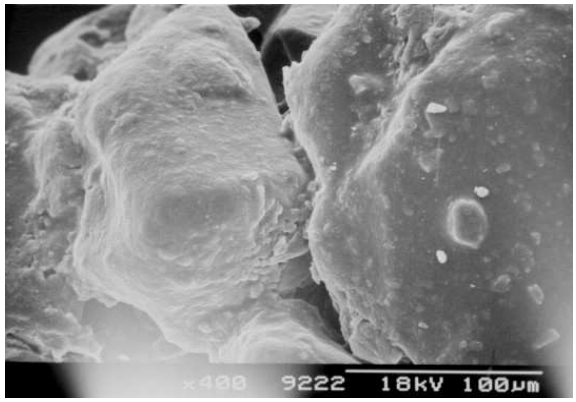


Fig. 3. SEM micrograph of Sample 1 (400×)

Samples 2 and 3 consist of powders with similar spreading coefficients (*Table 4.*). A parallelism was observed in the measured parameters too. The friability results are in agreement with the spreading coefficients. Essential differences cannot be observed between

the friabilities of Sample 2 and Sample 3 (*Table 5.*). However, there are differences in the porosity and the bulk and tapped densities of these two pellets. Sample 2 has a less friable, dense structure (*Figures 4. and 5.*) The parameters were improved as compared with Sample 1 through use of the excipient.

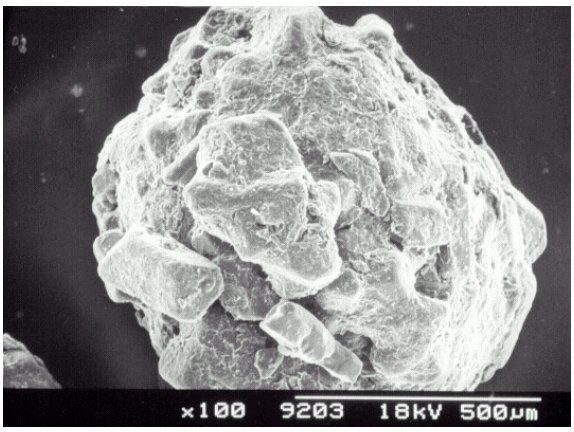


Fig. 4. SEM micrograph of Sample 2 (100×)

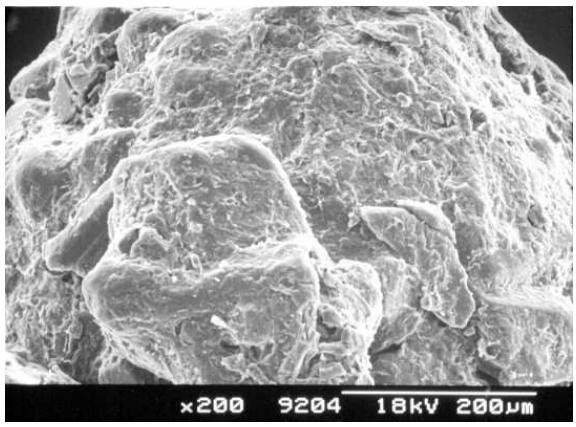


Fig. 5. SEM micrograph of Sample 2 (200×)

The friability and the bulk and tapped densities proved to be lower than those of the sample containing only metronidazole. The pellets are slightly porous. The particle size of Vivapur 101 is less than that of metronidazole. It was applied in the composition in a quantity of 25%. The binder solution spreads over the Vivapur 101 and metronidazole particles, but the same quantity of Klucel LF coats fewer particles in several layers. For Sample 3, the spreading coefficient of corn starch is higher and the particles (corn starch) are small. This composition and the amount of binder proved ideal.

The scanning electron micrographs (*Figures 6. and 7.*) reveal that the corn starch particles are enclosed among the larger metronidazole crystals. The pellet texture is dense, and the binder coats every particle. The binding forces are strong, and the friability is low.

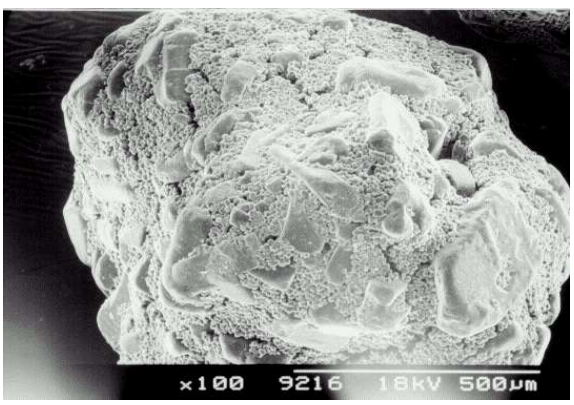


Fig. 6. SEM micrograph of Sample 3

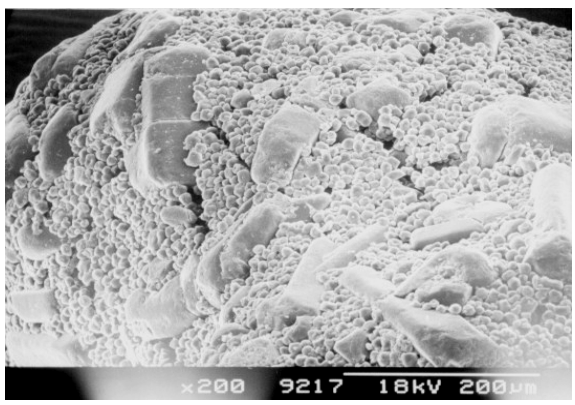
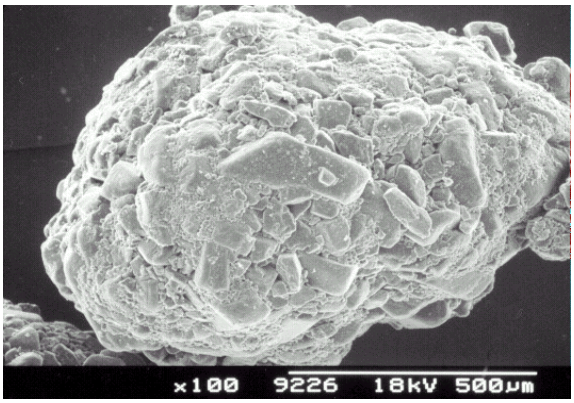


Fig. 7. SEM micrograph of Sample 3

(100×) *(200×)*



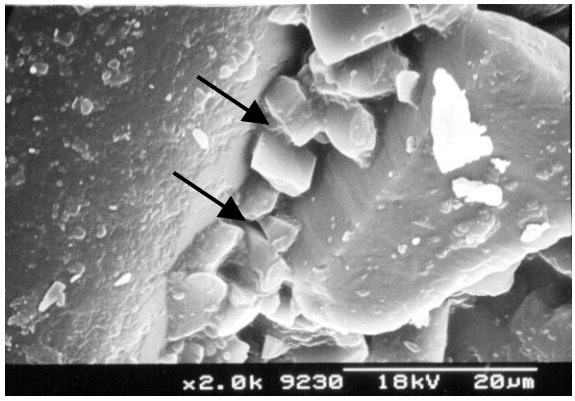


Fig. 8. SEM micrograph of Sample 4 (100×)

Fig. 9. SEM micrograph of Sample 4 (2000×)

Furthermore, the recrystallization of α-lactose monohydrate exerted a favourable influence on the parameters of Sample 4 (*Figures 8. and 9.*). The pellet texture is dense and slightly porous.

5.1.1. Conclusions

Connections can be observed between the friability and the spreading coefficient of the binder over the substrates, and the work of adhesion and cohesion between the particles when pellets are made from one- and two-component powder compositions. However, a knowledge of the particle size, the proportions of the components and the amount of binder is indispensable. A knowledge of the surface free energies of pharmaceutical powders and excipients, and of the work of adhesion and cohesion, can help in the processing of materials to make pellets. It plays an important part not only in the choice of a suitable binder, but also in that of appropriate excipients.

Direct correlations cannot be found between the surface free energy and the granule properties. Correlations can be expected between the spreading coefficients calculated from the surface free energy and the granule mechanical strength, and especially the friability. When the spreading coefficient of a binder over the substrate (S_{12}) is positive, the formation of dense, non-friable pellets can be expected (for two-component compositions, i.e. substrate + binder). However, the spreading coefficient results alone cannot predict the granule properties, especially in complex systems. Other factors play important roles, e.g. the particle size, the proportions of the components and the attractive effect between the particles. In spite of the fact that the binding agent spreads over the metronidazole (S_{12} = 12.2 mN/m) and low

friability is expected, the mechanical properties of granules containing only metronidazole are influenced by the work of cohesion of the binder, which coats the particles in several layers and is partly enclosed among the crystals. Samples 2 and 3 consist of powders with similar spreading coefficients; in both cases, the particle sizes of the excipients are smaller than that of the metronidazole. The small particles fill in the small holes and the binder is spread over the particles only in a thin layer because of the larger surface. For Samples 2 and 3, therefore, the work of adhesion is determining, which is larger than the work of cohesion of the binder. For Sample 4, the situation is similar to that for Samples 2 and 3, and the recrystallization of α-lactose monohydrate exerted a favourable influence on the parameters.

Overall, it was concluded that, in the course of the growth of the pellets, the particle sizes of the pharmaceutical powders and the interactions between the particles are important. If the work of cohesion of the binder is lower than that of the substrate and the work of adhesion between the particles, then the optimal amount of the binding agent is that which coats the particles in only one uniform and continuous layer.

5.2. Effect of proportion of excipient on surface free energy of powder mixtures

Investigations were made of whether the surface free energy of a powder mixture depends on the proportions of the components, and how the forces of cohesion and adhesion between the particles affect their interactions as functions of the proportions of the components. Metronidazole - corn starch powder mixtures were investigated. From these mixtures pellets were made, and are reported on in section 5.3. **[140]**. Connections were sought between the compositions of the powder mixtures, the physico-chemical character, the interparticle attractive forces and the parameters of the pellets produced.

5.2.1. Contact angle and surface free energy

The compositions of the powder mixtures prepared are shown in *Table 7.* The corn starch content of the mixtures was 25, 35, 50, 65 and 75%, respectively.

Table 7.

Compositions of powder mixtures

	Mix25	Mix35	Mix50	Mix65	Mix75
Metronidazole	750 g	650 g	500 g	350 g	250 g

Corn starch	250 g	350 g	500 g	650 g	750 g

The contact angles of the mixtures and of the components were measured in a polar (glycerol) and in an apolar (diiodomethane) liquid. The values of surface free energy and spreading coefficient were calculated from these results. Both the glycerol and the diiodomethane contact angles exhibited a decreasing tendency as the corn starch content was increased (*Table 8.*). In the series of data, the Mix50 contact angles differed from this tendency.

The measured contact angle of a compact is an average characteristic parameter which is influenced by the particles on the surface. The surface free energy of a powder mixture is affected by the individual contact angles of the materials and the interactions between them. Although there is not a considerable difference between the total surface free energies of the two components of the mixtures (metronidazole 56.6 mN/m and corn starch 62.3 mN/m) (*Table 8.*), the data for the mixtures showed a transition between that of the active agent and that of the excipient. The results for Mix50 were again different from the characteristic tendency in this case. The deviation can be seen in the polarity of Mix50 (17.2%).

Table 8.

Contact angles, surface free energies and polarity results for metronidazole, corn starch, Klucel LF and powder mixtures

	Contact angle (°)		Surface free energy (mN/m)			
	glycerol	diiodomethane	γ_s	γ_s^d	γ_s^p	Polarity (%)
Metronidazole	48.8 (± 1.3)	22.8 (± 1.7)	56.6	47.0	9.6	17.0
Mix25	42.2 (± 3.8)	16.0 (± 1.1)	60.3	48.9	11.4	18.9
Mix35	41.2 (± 1.5)	14.7 (± 1.0)	60.9	49.2	11.7	19.2
Mix50	45.6 (± 2.1)	14.9 (± 1.7)	59.3	49.1	10.2	17.2
Mix65	38.6 (± 2.0)	12.7 (± 1.7)	62.0	49.6	12.4	20.0
Mix75	37.0 (± 4.1)	11.5 (± 2.2)	62.7	49.8	12.9	20.6

Corn starch	37.5 (± 3.6)	11.2 (± 1.3)	62.3	49.9	12.4	19.9
*Klucel LF**	*70.1 (±1.5)*	*28.6 (±1.3)*	*47.9*	*45.0*	*2.9*	*6.1*

**Klucel LF data were applied to calculate the S results.*

5.2.2. Cohesiveness

In order to obtain additional information, and to explain the slight deviations in the surface free energy data, larger masses of the powder mixtures were also investigated. Determination of the compactibility of powders and powder mixtures provides information on the cohesiveness (and the adhesion properties). The cohesiveness data can be seen in *Figure 10.* Mix65 had the highest value of the constant 1/b, indicating the highest cohesiveness. The values for the other mixtures vary with the W_a and W_c data.

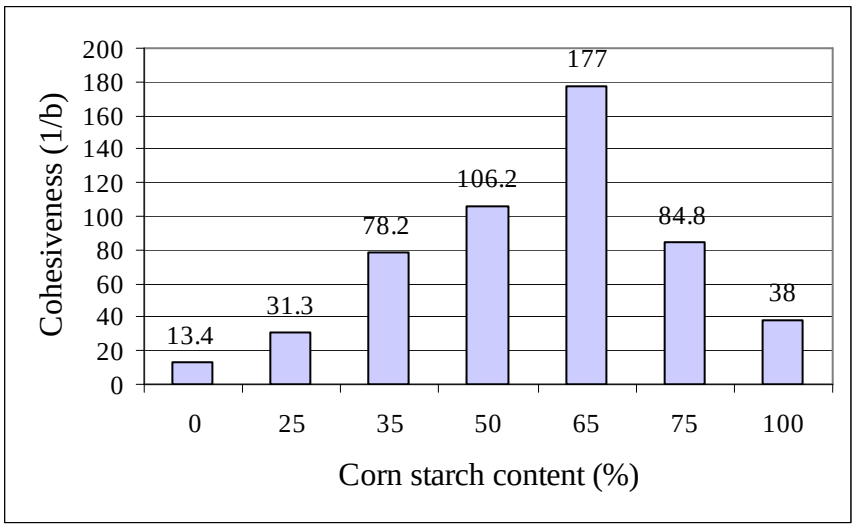


Fig. 10. Cohesiveness of samples as a function of corn starch content (R>0.994)

5.2.3. Scanning electron micrographs

The scanning electron micrographs of the mixtures were analysed. The forces of adhesion and cohesion between the particles were examined. The S_{12} and S_{21} values determined via W_a and W_c revealed that the metronidazole spread over the corn starch particles, because S_{12} was positive and S_{21} negative. The coefficient of spreading of metronidazole (1) over corn starch (2) was 5.2 mN/m, and that of corn starch over metronidazole was -6.1 mN/m. (This phenomenon can not be discerned clearly visually because of the difference in order of magnitude of the dimensions of the particles: metronidazole: length: 194 μm, breadth: 104 μm, corn starch: 12 μm in diameter.) W_a and W_c indicate that the attraction is strongest between the corn starch particles and weakest between

the metronidazole crystals (*Table 9.*). The metronidazole - corn starch W_a is intermediate between the two other data. It is well known from the literature that W_c between corn starch particles is fairly strong [141].

Table 9.

Work of cohesion and adhesion (mN/m)

	W_c	W_a (Metr)
Metronidazole	113.3	-
Corn starch	124.5	118.4

W_c: work of cohesion

W_a (Metr): work of adhesion between metronidazole and corn starch

Differences can be seen in the scanning electron micrographs of the mixtures containing different amounts of corn starch, in the different mixtures the interactions (adhesion and cohesion) being manifested differently. In Mix25, the relatively small amount of corn starch can be found on the surface of the metronidazole crystals, in consequence of the adhesion (*Figure 11.*).

In Mix35, the metronidazole crystals are nearly totally covered by one layer of corn starch particles (*Figure 12.*). The distribution of corn starch particles is even on the surface of metronidazole crystals. In Mix50, the corn starch particles are to be seen mainly on the surface of the metronidazole in consequence of adhesion forces. In the active regions on the edges and peaks, there are corn starch aggregates. Additionally, there are a few corn starch aggregates among the metronidazole crystals (*Figure 13.).*

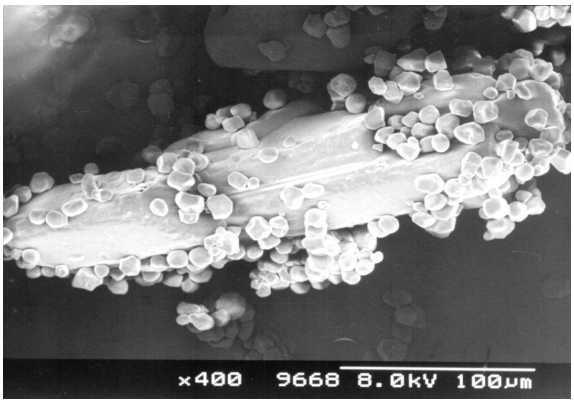


Fig. 11. SEM micrograph of Mix 25 (400×)

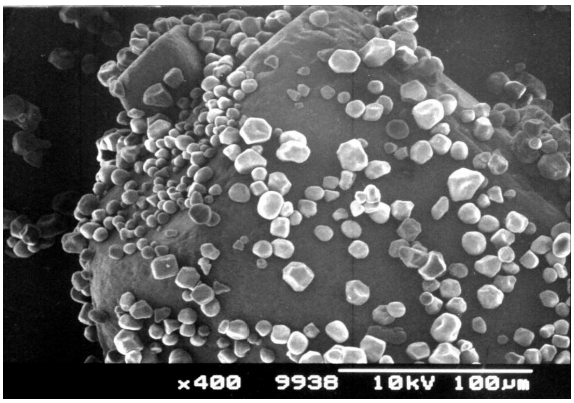


Fig. 12. SEM micrograph of Mix 35 (400×)

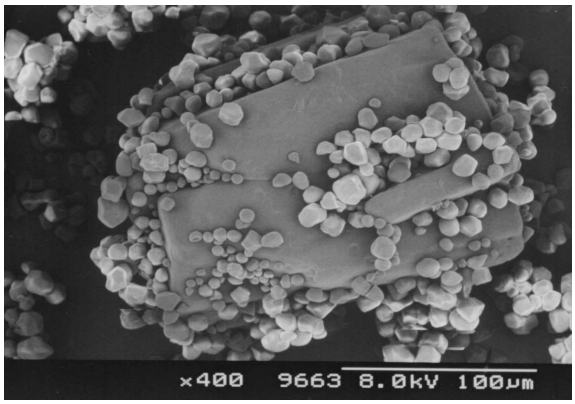


Fig. 13. SEM micrograph of Mix 50 (400×)

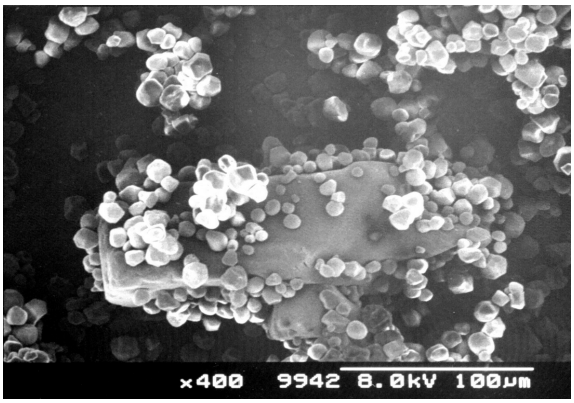


Fig. 14. SEM micrograph of Mix 65 (400×)

In Mix65, the corn starch particles are partly situated on the metronidazole surface and partly form aggregates. The amount of aggregates is larger here (*Figure 14.*). In contrast with our expectations, there is less corn starch on the surface of the metronidazole in Mix75 as compared with Mix50 (or Mix65). The remainder of the corn starch can be seen forming a few smaller aggregates around the metronidazole (*Figure 15.*). The reason lies in the higher degree of cohesion between corn starch particles because of the higher amount of corn starch.

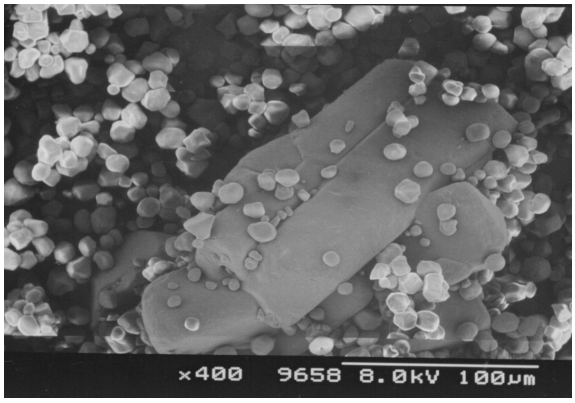


Fig. 15. SEM micrograph of Mix 75 (400×)

A transition can be observed between Mix50 and Mix65. Accordingly, for a corn starch content over 50%, the cohesion between the corn starch particles is determinative. The corn starch particles attract one another rather than the metronidazole crystals, and form small aggregates.

5.2.4. Conclusions

A multisided approach promotes an understanding of why the cohesiveness of Mix65 was so high. The cohesiveness results and the scanning electron micrographs point to a transition between Mix50 and Mix65. These data indicate the need to take into consideration

the proportions of the components, which may affect the interactions between the particles. Slight changes in the proportions of the components may induce significant alterations in the interactions between the particles. The scanning electron micrographs of Mix50 and Mix65 reveal that most of the corn starch in these mixtures is situated on the surface of the metronidazole, forming corn starch - metronidazole aggregates. This phenomenon is more marked for Mix65, where there are more corn starch aggregates on the surface of the metronidazole crystals. The high cohesiveness of this sample can be explained in terms of this fact.

But why only in this case? For a simple model, the situation may be as follows, as supported by the W_c, W_a and S values:

1. A little corn starch + a relatively large amount of metronidazole: all the corn starch particles are situated on the surface of the metronidazole.
2. More corn starch + a little less metronidazole: nearly all the corn starch particles are situated on the surface of the crystals, composing corn starch-covered aggregates, but some individual corn starch particles can also be observed.
3. A large amount of corn starch + a little metronidazole: more corn starch aggregates are formed due to the relative higher degree of cohesion between the corn starch particles. Accordingly, less adheres to the metronidazole, with weaker adhesion.

The examination of the given systems revealed that Mix50 best fits model 2, i.e. the bulk of the corn starch in the mixture adheres to the metronidazole surface. Mix25 and Mix35 conform to model 1, and Mix75 to model 3. Mix65 is intermediate between model 2 and model 3, this being a special case of the interactions, stemming from the proportions of the components. This phenomenon was revealed by a surface investigation of the mixtures, and was explained by the analysis of scanning electron micrographs and the cohesiveness data from the Kawakita equation.

5.3. Investigations of pellets prepared from powder mixtures

Pellets were produced from the mixtures investigated, and are reported on in section 5.2. (The preparation of the pellets was carried out according to section 4.2.3. The binder solution used was in every case 400 g 10% aqueous solution of Klucel LF.) Connections were sought between the compositions of the powder mixtures, the physico-chemical character, the interparticle attractive forces and the parameters of the pellets produced. The pellets were evaluated by considering the mechanical properties (friability and breaking strength) and

other pellet parameters (bulk and tapped densities and porosity). The pellet samples were denoted P25-P75, similarly to the notations of the mixtures.

5.3.1. Interparticular forces

First, the probable spreading of the binding agent on the surface of the mixtures was investigated. The probable mechanical properties of the pellets were estimated from the S data. These results can account for the properties of the pellets produced. The S values for the mixtures, metronidazole and corn starch are presented in *Table 10*.

It may be seen that the coefficient of spreading of Klucel LF (1) over the substrate (2) (S_{12}) is positive in every case, while that of the substrate over the binder (S_{21}) is negative. Further it may be stated that S_{12} increased and S_{21} decreased as the corn starch content of the mixtures was elevated. For this reason, the spreading of the binder over the surface of the powder mixtures becomes increasingly favoured. The S results for the powder mixtures are intermediate between those for metronidazole and those for corn starch. For the samples containing more corn starch, the S values indicate that pellets with low friability are to be expected if the prediction from the S values is applicable for systems more complex than binary systems.

When the spreading coefficient of a binder over the substrate (S_{12}) is positive, the formation of dense, non-friable pellets can be expected. The friability of the pellets is influenced by the interactions between the particles. The interactions between the particles are influenced by the W_a and W_c data, which are given in *Table 11*. (Some overlap can be found in these data with the data in section 5.1., but the repetition seems to be necessary with these supplementary data.)

Table 10.

Spreading coefficients of Klucel LF over substrates (S_{12}), and of drug over Klucel LF (S_{21}) (mN/m)

Binder (1)	Substrate (2)	S_{12} (Klucel LF (1))	S_{21} (Klucel LF (1))
Klucel LF	Metronidazole	5.12	-12.42
Klucel LF	Mix25	7.21	-17.65
Klucel LF	Mix35	7.51	-18.41
Klucel LF	Mix50	7.21	-15.63
Klucel LF	Mix65	8.01	-20.29
Klucel LF	Mix75	8.27	-21.39
Klucel LF	Corn starch	8.25	-20.53

Table 11.

Work of cohesion and adhesion (mN/m)

	W_c	W_a (Metr)	W_a (Klu LF)
Metronidazole	113.3	-	100.8
Corn starch	124.5	118.4	103.9
Klucel LF	95.7	-	-

W_c: work of cohesion

W_a (Metr): work of adhesion between metronidazole and corn starch

W_a (Klu LF): work of adhesion between binder and substrates

5.3.2. Pellet properties

For the metronidazole - corn starch - hydroxypropylcellulose systems, the work of cohesion of the binder is lower than that of the substrate, and this favours the binder spreading over the substrate. W_a between the binder and substrates is in every case higher than the W_c of Klucel LF and this too helps the binder to spread over the substrate.

However, differences are observed between these values. W_a between corn starch and Klucel LF is higher than that between metronidazole and Klucel LF. Accordingly, W_a between the substrates (inside the pellet powder mixture) was calculated and compared with the W_c of the substrate and binder. W_a for the excipient - metronidazole composition is higher than W_c for Klucel LF. The binder spreads over the substrate in this case too.

The friability and breaking strength of the pellets are listed in *Table 12*. The pellet friability tended to increase as the corn starch content was increased, in contrast with the prediction made from the S data.

Table 12.

Mechanical properties of pellets

	Friability (%)	Breaking strength (N)
P25	11.5 (± 1.7)	1.43 (± 0.16)
P35	12.4 (± 0.8)	1.32 (± 0.13)
P50	9.2 (± 1.6)	1.32 (± 0.21)
P65	16.6 (± 4.5)	1.21 (± 0.18)
P75	15.4 (± 0.5)	1.17 (± 0.14)

The breaking strength *(Table 12.)* exhibited a decreasing tendency, in accordance with the friability data. Thus, the mechanical properties of the pellets became more unfavourable as S_{12} increased. The friability values of P50 and P65 differed significantly. The friability of the pellets was more significant at a corn starch content over 50%. The different data of P50 draw attention to the fact that the proportions of the active agent and the excipient and the amount of the binder used were ideal. The surface of the particles is coated with the binder solution only in one continuous layer, which is thin enough for the binder - substrate adhesion to be dominant.

The bulk and tapped densities of the pellets were also tested. It is clear from the results that they decreased as the corn starch content was increased (*Figure 16.*). The porosity of the

pellets was calculated and it may be seen that they had a looser, more porous structure. An increasing tendency can be detected in the porosity results as the corn starch content was increased (*Figure 17.*). The difference in the porosity of the samples was significant.

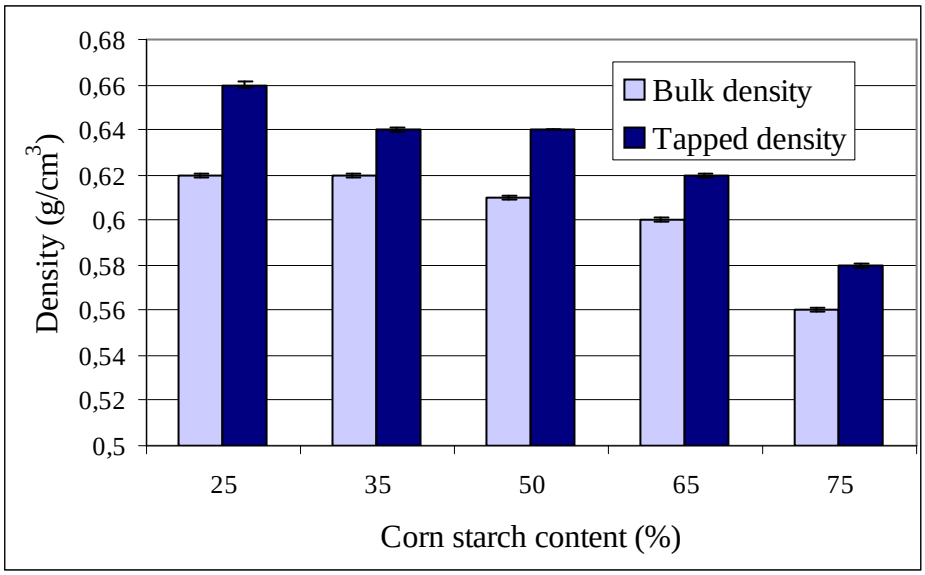


Fig. 16. Bulk and tapped densities of pellets

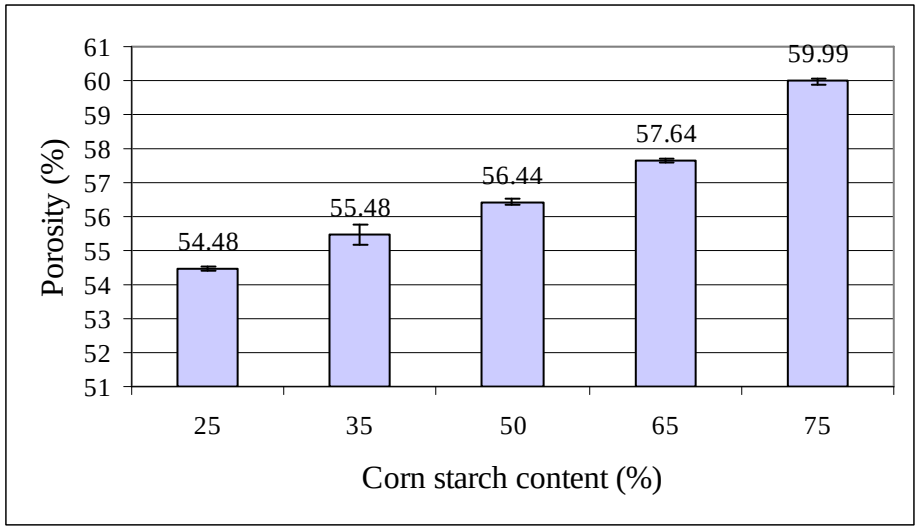


Fig. 17. Porosity of the pellets

5.3.3. Scanning electron micrographs

Scanning electron micrographs were also prepared for a better understanding of the phenomena observed. P25 contains 25% corn starch and 75% metronidazole. The pellet texture is dense, but slightly porous (*Figures 18. and 19.*). The scanning electron micrographs reveal that the corn starch particles are enclosed among the larger metronidazole crystals. Many metronidazole crystals can be seen on the surface of the pellets due to the large

metronidazole content.

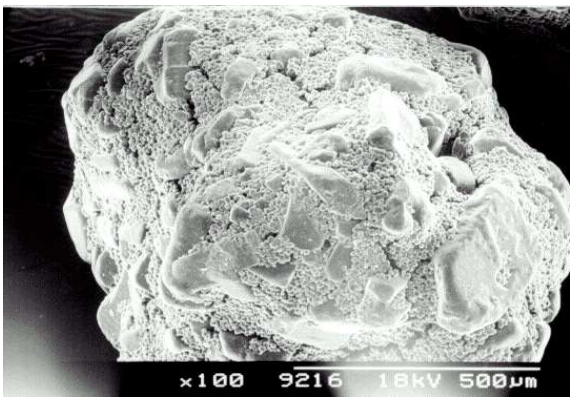


Fig. 18. SEM micrograph of P25 (100×)

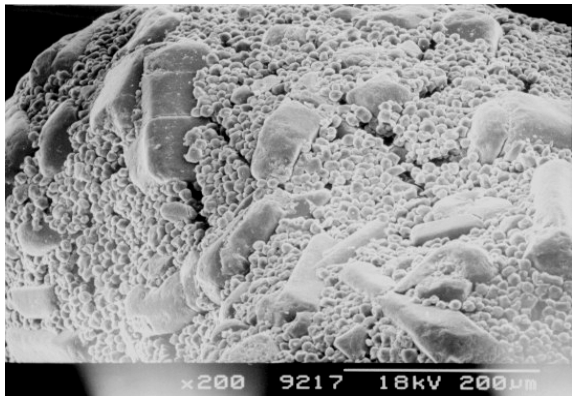


Fig.19. SEM micrograph of P25 (200×)

P35 (*Figures 20. and 21.*) and P50 (*Figures 22. and 23.*) contain more corn starch than P25. Due to the higher corn starch content, the surface of the metronidazole crystals was extensively covered with small corn starch particles. The tendency which was found in the investigations of the powder mixtures can also be seen in the scanning electron micrographs of the pellets.

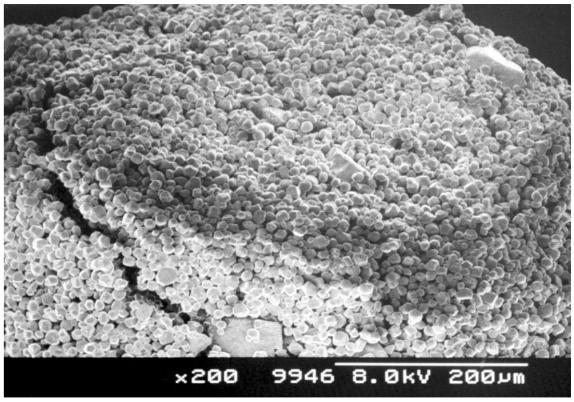


Fig. 20. SEM micrograph of P35 (200×)

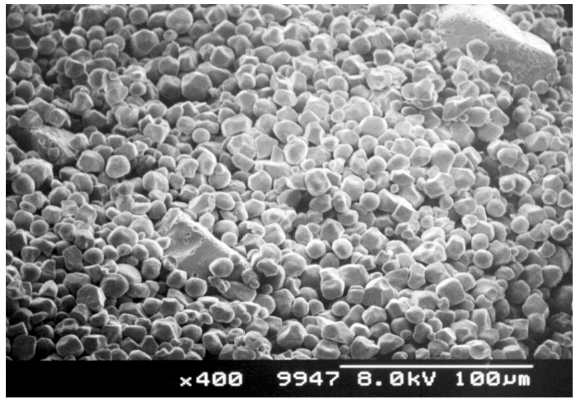


Fig. 21. SEM micrograph of P35 (400×)

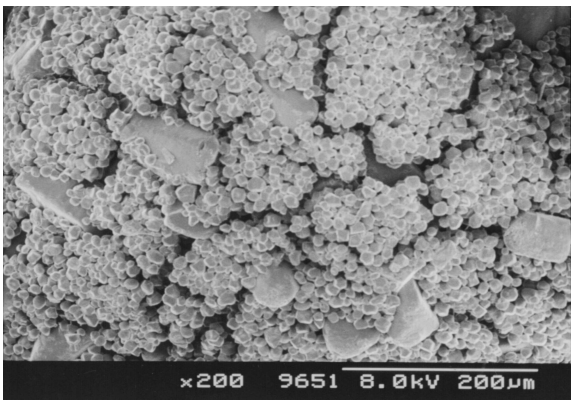


Fig. 22. SEM micrograph of P50 (200×)

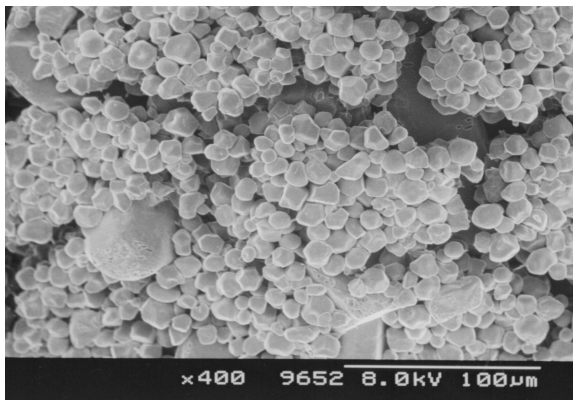


Fig. 23. SEM micrograph of P50 (400×)

P65 (*Figures 24. and 25.*) and P75 (*Figures 26. and 27.*) contain more corn starch than the other pellets. The distribution of the corn starch particles in these pellets exhibits specific features, in accord with the distribution of the components in the mixtures. The pellet texture is more porous: more gaps and craters may be seen in the texture of the pellets containing more corn starch. These gaps can be observed on the border of the metronidazole – corn starch aggregates.

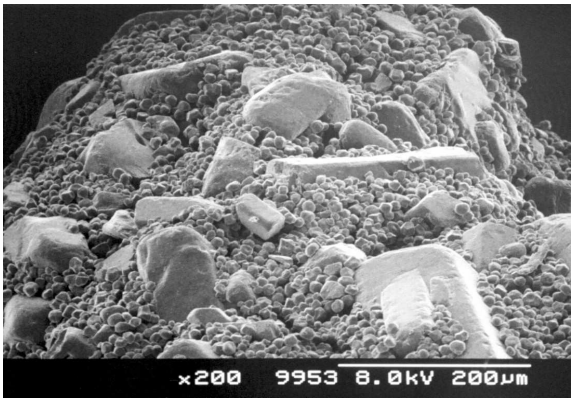


Fig. 24. SEM micrograph of P65 (200×)

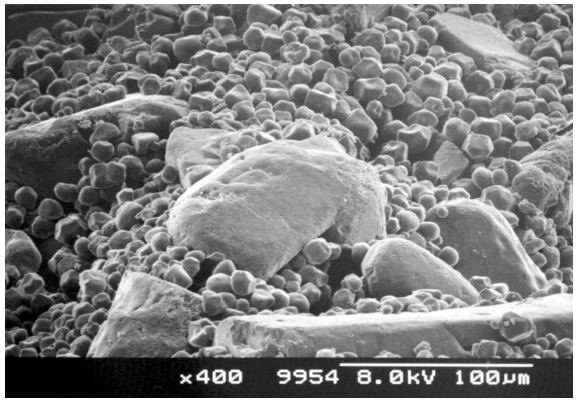


Fig.25. SEM micrograph of P65 (400×)

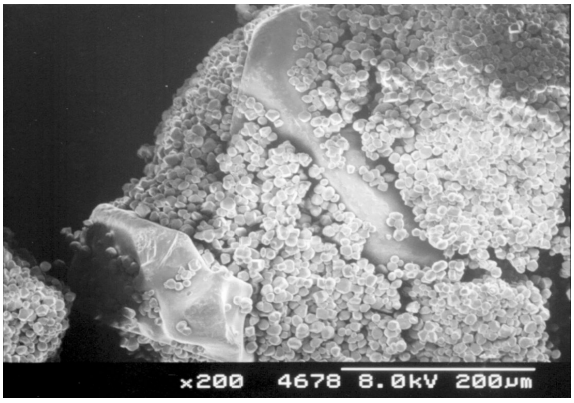


Fig. 26. SEM micrograph of P75 (200×)

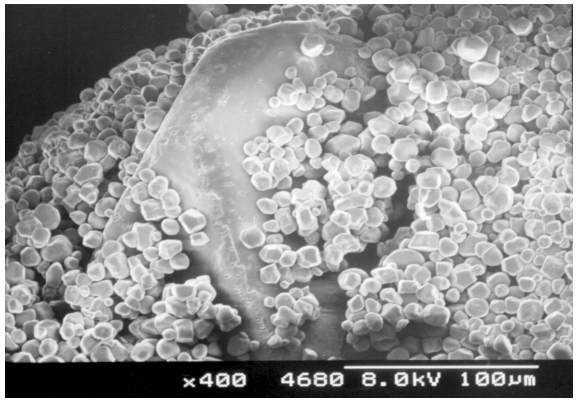


Fig.27. SEM micrograph of P75 (400×)

The surface of the metronidazole crystals is not covered with corn starch. Accordingly, the surface of the crystals can be seen in the scanning electron micrographs. The corn starch particles stick to one other partly through cohesion and partly through binder - corn starch adhesion.

The pellet particles produced differed in composition, particularly in the event of a higher corn starch content. Some particles contained more metronidazole, and others less. The distribution of the components was not homogeneous. Accordingly, in the SEM micrographs of some pellets, more metronidazole could be seen on the surface in spite of the higher corn

starch content. This was due in great part to the W_a and W_c between the particles, similarly as observed for the powder mixtures.

The pellet parameters were also influenced by the amount of the binder solution. The same quantity of binder solution was used for pelletization in every case. Compositions containing more small corn starch particles possess a larger surface area. Accordingly, more binder solution was necessary to cover the particles and to cause them to stick them together. Above a critical limit, the amount of the binder solution was not sufficient to ensure the coverage of the particles. For this reason, the mechanical properties of the pellets containing higher quantities of excipient were unfavourable.

5.3.4. Conclusions

The experiments reported here indicate that, in the course of the processing of powder mixtures, it is very important to take into consideration the proportions of the components. The cohesiveness (1/b) and scanning electron micrographs of Mix50 and Mix65 draw attention to the composition dependence of the mixtures, which is expressed in γ_s and the polarity. In powder mixtures, the interactions between the particles are determined by the forces of adhesion and cohesion. The surface free energy data for mixtures are not always directly proportional to those of the components.

For more complex systems, S cannot be utilized to predict the mechanical properties of the pellets. For the samples investigated here, it may be stated that, as the surface free energy values of the mixtures increased and the binder - mixture S values increased (the corn starch content increased), the mechanical properties of the pellets produced (friability and breaking strength) became more unfavourable. The bulk and tapped densities of the pellets decreased and the porosity increased as the corn starch content increased, and the granules had a looser, more porous structure. Consequently, in contrast with the predictions from the S values, pellets with a more porous and looser texture and with unfavourable mechanical properties can be produced as the S_{12} values increase. The pellets containing less corn starch (P25 and P35) proved to be ideal compositions. The compositions of these pellets were homogeneous. In these cases, the work of cohesion of the corn starch was not dominant. The interactions between the particles were determined by the adhesion between the corn starch and the metronidazole. The pellet compositions can be designed with consideration of the particle size and surface, the interactions arising and the amount of binder solution applied. Thus, the mechanical properties of pellets can be predicted from S data only with reservations, for relatively simple systems.

6. Summary

The aims of the work were to investigate the role of the surface free energy in the selection of the suitable excipient, and to examine whether the surface free energy of a powder mixture depends on the proportions of the components, and how the forces of cohesion and adhesion between the particles affect their interactions as functions of the proportions of the components.

Major conclusions:

- The build-up of the pellets, their structure and the interactions between the powder particles can be studied according to a new aspect by using the surface free energy data.
- The surface free energies of pharmaceutical powders and excipients, and the work of adhesion and cohesion, play important roles in the choice of a suitable binder and appropriate excipients.
- The spreading coefficient results alone cannot predict the granule properties, especially in complex systems.
- In spite of the fact that the binding agent spreads over the metronidazole and low friability is expected, the mechanical properties of granules containing only metronidazole are influenced by the work of cohesion of the binder, which coats the particles in several layers and is partly enclosed among the crystals.
- If the work of cohesion of the binder is lower than that of the substrate and the work of adhesion between the particles, then the optimal amount of the binding agent is that which coats the particles in only one uniform and continuous layer.
- W_a and W_c indicate that the attraction is strongest between the corn starch particles and weakest between the metronidazole crystals. The metronidazole - corn starch W_a is intermediate between the two other data.
- Differences can be seen in the scanning electron micrographs of the mixtures containing different amounts of corn starch, the interactions (adhesion and cohesion) being manifested differently in the different mixtures. For a corn starch content over 50%, the cohesion between the corn starch particles is determinative. The corn starch particles attract one another rather than the metronidazole crystals, and form small aggregates.
- The pellet friability tended to increase as the corn starch content was increased, in contrast with the prediction made from the S data. The breaking strength exhibited a

decreasing tendency, in accordance with the friability data. Thus, the mechanical properties of the pellets became more unfavourable as S_{12} increased.

- The bulk and tapped densities of the pellets decreased as the corn starch content was increased. The pellets had a looser, more porous structure. An increasing tendency can be detected in the porosity results as the corn starch content was increased.
- The pellet particles produced differed in composition, particularly in the event of a higher corn starch content. Some particles contained more metronidazole, and others less. The distribution of the components was not homogeneous. This was due in great part to the W_a and W_c between the particles, similarly as observed for the powder mixtures.
- Above a critical limit, the amount of the binder solution was not sufficient to ensure the coverage of the particles. For this reason, the mechanical properties of the pellets containing higher quantities of excipient were unfavourable.
- For more complex systems, S cannot be utilized to predict the mechanical properties of the pellets.
- Consequently, in contrast with the predictions from the S values, pellets with a more porous and looser texture and with unfavourable mechanical properties can be produced as the S_{12} values increase. The pellets containing less corn starch (P25 and P35) proved to be ideal compositions. The compositions of these pellets were homogeneous.

Practical usefulness:

The use of the surface free energy may be a new aspect in the selection of suitable excipients in the course of pelletization. The suitable excipients can be selected on the basis of the binder - substrate spreading coefficient values. The choice of an excipient with a higher S value is suggested, instead of an excipient with a low spreading coefficient. In this case the given binder will spread on the surface of the excipient. The interactions between the particles can be investigated by evaluating the Wa and Wc data.

If the work of cohesion of the binder is lower than that of the substrate and the work of adhesion between the particles, then the optimal amount of the binding agent is that which coats the particles in only one uniform and continuous layer. The mechanical properties of the pellets are in this case optimal.

Investigation of the scanning electron micrographs of the powder mixtures used during the pelletization can prognosticate the problems arising during the pellet making.

Inhomogeneous distribution in the powder mixture can produce pellet particles with different compositions.

The spreading coefficient results alone cannot predict the granule mechanical properties, especially in complex systems. Other factors play important roles, e.g. the particle size, the proportions of the components, the amount of the binder and the attractive effect between the particles. However, the use of S values and other factors can complement one other and they can therefore be applied in the course of the industrial development.

The structure and the mechanical properties of the pellets are determinative from the aspect of the further processing. The pellets need a certain mechanical strength in order to resist the force arising during the further processing in the course of the coating of the particles, during capsule filling or also during tabletting.

The data calculated from the surface free energy give important information for the practice of pelletization. This information can be used during the development of a new pharmaceutical dosage form. Furthermore, it is of value during the industrial processing in order to solve different technological problems which may arise during that stage.

7. References

[1] Buckton, G., J. Pharm. Pharmacol., **47**, 265 (1995)

[2] Göttner, G. H., Einführung in die Schmierungstechnik., Karl Marklein Verl., Düsseldorf (1966)

[3] Prescott, J. K., Barnum, R. A., Pharmaceutical Technology Europe, **13**, 36 (2001)

[4] Ahfat, N. M., Buckton, G., Burrows, R., Ticehurst, M. D., Int. J. Pharm., **156**, 89 (1997)

[5] Rowe, R. C., Int. J. Pharm., **53**, 75 (1989)

[6] Rowe, R. C., Int. J. Pharm., **58**, 209 (1990)

[7] Zajic, L., Buckton, G., Int. J. Pharm., **59**, 155 (1990)

[8] Podczeck, F., Int. J. Pharm., **178**, 93 (1999)

[9] Podczeck, F., Pharmaceutical Technology Europe, **11**, 16 (1999)

[10] Podczeck, F., Pharmaceutical Technology Europe, **11**, 34 (1999)

[11] Prescott, J. K., Barnum, R. A., Pharmaceutical Technology Europe, **13**, 44 (2001)

[12] Bajdik, J., Pintye-Hódi, K., Planinšek, O., Regdon, G. Jr., Dreu, R., Srčič, S., Erős, I., Int. J. Pharm., **269**, 393 (2004)

[13] Sherrington, P. I., Oliver, R., Granulation, Heyden, London (1981)

[14] Ghebre-Sellassie, I., Pharmaceutical Pelletization Technology, Warner-Lambert Company, Morris Plains, New Jersey (1989)

[15] Ghebre-Sellassie, I., Multiparticulate Oral Drug Delivery, Marcel Dekker, New York (1994)

[16] Rácz, I., Selmeczi, B., Gyógyszertechnológia, 3. kötet, Medicina, Budapest (2001)

[17] Wauters, P. A. L., Jakobsen, R. B., Litster, J. D., Meesters, G. M. H., Scarlett, B., Powder Technol. **123**, 166 (2002)

[18] Pietsch, W., Agglomeration Processes, Phenomena, Technologies, Equipment, Wiley-VCH Verlag GmbH, Weinheim (2002)

[19] Pandula, E., Takács, G., Ipari gyógyszerészet, Medicina, Budapest (1964)

[20] Gyarmathy, M., Hasznos, L., Gyógyszerészet, **38**, 891 (1994)

[21] Gyarmathy, M., Gyógyszerészet, **37**, 767 (1993)

[22] Parikh, D. M., Handbook of Pharmaceutical Granulation Technology, Marcel Dekker, New York (1997)

[23] Pont, V., Saleh, K., Steinmetz, D., Hemati, M., Powder Technol., 120, 97 (2001)

[24] Faure, A., York, P., Rowe, R. C., Eur. J. Pharm. Biopharm., **52**, 269 (2001)

[25] Muskó, Zs., Pintye-Hódi, K., Gáspár, R., Pintye, J., Szabó-Révész, P., Erős, I., Falkay, G., Eur. J. Pharm. Biopharm., **51**, 143 (2001)

[26] Harun Ar Rashid, Heinämäki, J., Antikainen, O., Yliruusi, J., Eur. J. Pharm. Biopharm., **51**, 227 (2001)

[27] Swarbrick, J., Boylan, J.C., Encyclopedia of Pharmaceutical Technology, 2nd Edition, Volume 3, Marcel Dekker, New York (2002)

[28] Vervaet, C., Baert, L., Remon, J. P., Int. J. Pharm., **116**, 131 (1995)

[29] Gyarmathy, M., Hasznos, L., Gyógyszerészet, **39**, 9 (1995)

[30] Schröder, M., Kleinebudde, P., Eur. J. Pharm. Sci., **4., Suppl. 1**, S182 (1996)

[31] Chatlappali, R., Rohera, B. D., Int. J. Pharm., **161**, 179 (1998)

[32] El Saleh, F., Jumaa, M., Hassan, I., Kleinebudde, P., STP Pharma Sci., **10** 379 (2000)

[33] Berggren, J., Alderborn, G., Int. J. Pharm., **219**, 113 (2001)

[34] Sousa, J. J., Sousa, A., Podczeck, J. M., Newton, J. M., Int. J. Pharm., **232**, 91 (2002)

[35] Gyarmathy, M., Gyógyszerészet, **37**, 845 (1993)

[36] Fekete, R., Marton, S., Farkas, E., Rácz, I., Pharmazie, **54**, 200 (1999)

[37] Ramaker, J. S., Fundamentals of the High-shear Pelletization Process, Stichting Drukkerij C. Regenboog, Groningen, The Netherlands (2001)

[38] Pepin, X., Blanchon, S., Couarraze, G., J. Pharm. Sci. US, **90**, 322 (2001)

[39] Pepin, X., Blanchon, S., Couarraze, G., J. Pharm. Sci. US, **90**, 332 (2001)

[40] Johansen, A., Schæfer, T., Eur. J. Pharm. Sci., **12**, 297 (2001)

[41] Sherif I. Farag Badawy, Munir A. Hussain, AAPS PharmSciTech, 2004; **5** (3) Article 38 (online only, http://www.aapspharmscitech.org)

[42] Aulton, M. E., Pharmaceutics. The Science of Dosage Form Design, 2nd Edition, Churchill Livingstone, London (2002)

[43] Schreiber, R., Vogt, C., Werther, J., Brunner, G., J. Supercrit. Fluid., **24**, 137 (2002)

[44] Gombás, Á., Szabóné Révész, P., Erős, I., Gyógyszerészet, **45**, 299 (2001)

[45] Pallagi, E., Vass, K., Pintye-Hódi, K., Kása, P. Jr., Falkay, G., Erős, I., Szabó-Révész, P., Eur. J. Pharm. Biopharm., **57**, 287 (2004)

[46] Gyarmathy, M., Gyógyszerészet, **37**, 851 (1993)

[47] Gyarmathy, M., Gyógyszerészet, **37**, 525 (1993)

[48] Erdey-Grúz, T., A fizikai kémia alapjai, 4. kiadás, Műszaki Könyvkiadó, Budapest (1972)

[49] Buckton, G., Powder Technol., **61**, 237 (1990)

[50] Lugscheider, E., Bobzin, K., Surf. Coat. Tech., **165**, 51 (2003)

[51] Erős, I., Gyógyszerészet, **26**, 90 (1982)

[52] Young, T., Phil. Trans. Roy. Soc. Lond., **9**, 255 (1805)

[53] Bonn, D., Ross, D., Rep. Prog. Phys.,**64**, 1085 (2001)

[54] Bonn, D., Ross, D., Bertrand, E., Ragil, K., Shahidzadeh, N., Broseta, D., Meunier, J., Physica A, **306**, 279 (2002)

[55] http://www.kruss.info/

[56] Chibowski, E., Perea-Carpio, R., Adv. Colloid Interfac., **98**, 245 (2002)

[57] Zissmann, W. A., Advances in Chemistry, **43**, 1 (1964)

[58] Fowkes, F. M., Ind. Eng. Chem., **56**, 40 (1964)

[59] Owens, D. K., Wendt, R. C., J. Appl. Polym. Sci., **13**, 1741 (1969)

[60] Rabel, W., Farbe und Lack, **77**, 997 (1971)

[61] Schultz, J., Tsutsumi, K., Donnet, J. B., J. Coll. Int. Sci., **59**, 272 (1977)

[62] Schultz, J., Tsutsumi, K., Donnet, J. B., J. Coll. Int. Sci., **59**, 277 (1977)

[63] Pepin, X., Blanchon, S., Couarraze, G., Int. J. Pharm., **152**, 1 (1997)

[64] Buckton, G., Drug. Dev. Ind. Pharm., **18**, 1149 (1992)

[65] Levoguer, C., Butler, D., Thielmann, F., Williams, D., Pharmaceutical Technology Europe, November, 36. (2000)

[66] Dove, J. W., Buckton, G., Doherty, C., Int. J. Pharm., **138**, 199 (1996)

[67] Planinšek, O., Trojak, A., Srčič, S., Int. J. Pharm., **221**, 211 (2001)

[68] Wu, S., J. Polym. Sci., **34**, 19 (1971)

[69] Wu, S., Brzorowski, K.J., J. Colloid Interface Sci., **37**, 686 (1971)

[70] Fowkes, F. M., J. Phys. Chem., **66**, 382 (1962)

[71] Fowkes, F. M., Wetting, Soc. Chem. Ind. Monograph 25, London (1967)

[72] Bajdik, J., **Tüske, Zs**., Hódi, K., Erős, I., Acta Pharmaceutika Hungarica **73**, 80 (2003)

[73] Hódi, K., **Tüske, Zs.**, Bajdik, J. Acta Pharmaceutika Hungarica **74**, 90 (2004)

[74] Good, R. J., J. Adhesion Sci. Technol., **6**, 1269 (1992)

[75] Van oss, C. J., Giese, R. F., Wu, W., J. Adhes., **63**, 71 (1997)

[76] Mohhamad, H. A. H., Fell, J. T., Int. J. Parm., **11**, 149 (1982)

[77] Ticehurst, M. D., Rowe, R. C., York, P., Int. J. Pharm., **111**, 241 (1994)

[78] Mukhopadhyay, P., Schreiber, H. P., Colloid. Surface A, **100**, 47 (1995)

[79] Ticehurst, M. D., York, P., Rowe, R. C., Dwivedi, S. K., Int. J. Pharm., **141**, 93 (1996)

[80] Feeley, J. C., York, P., Sumby, B. S., Dicks, H., Int. J. Pharm., **172**, 89 (1998)

[81] Grimsey, I. M., Sunkersett, M., Osborn, J. C., York, P., Rowe, R. C., Int. J. Pharm., **191**, 43 (1999)

[82] Ahfat, N. M., Buckton, G., Burrows, R., Ticehurst, M. D., Eur. J. Pharm. Sci., **9**, 271 (2000)

[83] Levoguer, C., Butler, D., Thielmann, F., Williams, D., Pharmaceutical Technology Europe, **12**, 36 (2000)

[84] Planinšek, O., Zadnik, J., Rozman, Š., Kunaver, M., Dreu, R., Srčič, S., Int. J. Pharm., **7404**, 1 (2003)

[85] Schultz, J., Lavielle, L., Martin, C., *J. Adhesion* **23**, 45 (1987)

[86] Schultz, J., Lavielle, L., In: Lloyd, D. R., Ward, T. C., Schreiber, H. P., Inverse Gas Chromatography of Polymers and Other Materials, ACS Symp. Ser. 391, p. 185, American Chemical Society, Washington DC, (1989)

[87] James, A. T., Martin, A. T. P., Biochem. J., **15**, 679 (1951)

[88] Rowe, R. C., Int. J. Pharm., **52**, 149 (1989)

[89] Israelachvili, J. N., Intermolecular and Surface Forces 2nd Edition, Academic Press, London (1992)

[90] Iveson, S. M., Lister, J. D., Hapgood, K., Ennis, B. J., Powder Technol., **117**, 3 (2001)

[91] Dupré, A., Theorie Mechanique de la Chaleur, Gauthier-Villars, Paris, (1869). In: Podczeck, F., Particle-Particle Adhesion in Pharmaceutical Powder Handling, Imperial College Press, London, (1998)

[92] Podczeck, F., Particle-Particle Adhesion in Pharmaceutical Powder Handling, Imperial College Press, London (1998)

[93] Lifshitz, E. M., Sov. Phys. JETP 2 73-83, (1956) In: Podczeck, F., Particle-Particle Adhesion in Pharmaceutical Powder Handling, Imperial College Press, London (1998)

[94] Zimon, A. D.: Adhesion of dust and powder. 2nd Edition, Consultant Bureau, New York (1982) In: Podczeck, F., Particle-Particle Adhesion in Pharmaceutical Powder Handling, Imperial College Press, London (1998)

[95] Zajic, L., Buckton, G., Int. J. Pharm., **59**, 155 (1990)

[96] Hancock, B. C., York, P., Rowe, R. C., Eur. J. Pharm. Sci., **2**, 205 (1994)

[97] Planinšek, O., Pišek, R., Trojak, A., Srčič, S., Int. J. Pharm., **207**, 77 (2000)

[98] Zhang, D., Flory, J. H., Panmai, S., Batra, U., Kaufman, M. J., Colloid. Surface A, **206**, 547 (2002)

[99] Zhang, D., Flory, J. H., Panmai, S., Batra, U., Kaufman, M. J., Colloid Surface A, **206**, 547 (2002)

[100] Bajdik, J., Pintye-Hódi, K., Planinšek, O., **Tüske, Zs**., Tasic, L., Regdon, G. Jr., Srčič, S., Erős, I., Drug Dev. Ind. Pharm. **30**, 381 (2004)

[101] Prime, D., Atkins, P.J., Slater, A., Sumby, B., Adv. Drug Deliver. Rev., **26**, 51 (1997)

[102] **Tüske, Zs**., Bajdik, J., Hódi, K., Erős, I., Acta Pharmaceutika Hungarica **73**, 86 (2003)

[103] Knoll, J., Gyógyszertan, Medicina, Budapest (1993)

[104] Mutschler, E., Derenorf, H., Drug Actions, Medpharm Scientific Publishers, Stuttgart (1995)

[105] Vizi, E. Sz., Humán farmakológia, Medicina, Budapest (1997)

[106] Fürst, Zs., Gyógyszertan, Medicina, Budapest (1998)

[107] Gyógyszer Kompendium 2005, CMPMedica Információs Kft., Budapest (2005)

[108] Gennaro, A. R., Remingston's Pharmaceutical Sciences, 17th Edition, Mack Printing Company, Easton, Pennsylvania (1985)

[109] Deutsches Arzneibuch. 10. Ausgabe. Band 3., Deutscher Apotheker Verlag, Stuttgart (1991)

[110] Index Nominum, International Drug Directory, Edited by Swiss Pharmaceutical Society, Medpharm Scientific Publishers, Stuttgart (1992)

[111] USP XXIII, The United States Pharmacopoeia, United States Pharmacopeial Convention Inc., Twinbrook Parkway, Rockville, MD., (1995)

[112] British Pharmacopoeia 1998, The Stationery Office, London (1998)

[113] European Pharmacopoeia, 4th Edition, Council of Europe, Strasbourg (2001)

[114] Rote Liste, Arzneimittelverzeichnis für Deutschland, Rote Liste Service GmbH, Frankfurt a.M. (2002)

[115] Sean C Sweetman, Martindale. The Complete Drug Reference, 33rd Edition, Pharmaceutical Press, London (2002)

[116] Rowe, R. C., Sheskey, P. J., Weller, P. J., Handbook of Pharmaceutical Excipients, 4th Edition, Pharmaceutical Press and American Pharmaceutical Association, London (2003)

[117] Grose, L., STP. Pharma Sci., **6**, 83 (1990)

[118] Law, M. F., Deasy, P. B., Eur. J. Pharm. Biopharm., **45**, 57 (1998)

[119] Lindahl, A., Persson, B., Ungell, A. L., Lennernas, H., Pharm. Res., **16**, 97 (1999)

[120] Acquier, R., Hamdani, H., Moillols, H., Delonca, H., Pharm. Acta Helv., **67**, 315 (1992)

[121] Wesley, L. A., Drug. Dev. Ind. Pharm., **18**, 599 (1992)

[122] Kitamori, N., Makino, T., Drug. Dev. Ind. Pharm., **8**, 125 (1982)

[123] Rudnic, E. M., Rhodes, C. T., Welch, S., Bernardo, P., Drug. Dev. Ind. Pharm., **8**, 87 (1982)

[124] Weiner, M., Bernstein, I. L., Adverse Reactions to Drug Formulation Agents: a Handbook of Excipients, Marcel Dekker Inc., New York (1989)

[125] Kottke, M. K., Chueh, H. R., Rhodes, C. T., Drug. Dev. Ind. Pharm., **18**, 2207 (1992)

[126] Wade, A., Weller, P. J., Handbook of Pharmaceutical Excipients, 2nd Edition, American Pharmaceutical Association, Washington (1994)

[127] Omray A, Omray P. Indian J. Pharm. Sci., **48**, 20 (1986)

[128] K121 Contact Angle and Adsorption Measuring System, Users Manual, Krüss GmbH, Hamburg (1996)

[129] Buckton, G., Newton, J. M., J. Pharm. Pharmacol., **37**, 605 (1985)

[130] Sheridan, P. L., Buckton, G., Storey, D. E., Int. J. Pharm., **109**, 155 (1994)

[131] Muster, T. H., Prestidge, C. A., Int. J. Pharm., **234**, 43 (2002)

[132] Podczeck, F., Rahman, S. R., Newton, J. M., Int. J. Pharm., **192**, 123 (1999)

[133] Beddow, J. K., Particle Characterization in Technology, Volume I. Applications and Microanalysis, CRC Press, Boca Raton, Florida (1984)

[134] Beddow, J. K., Particle Characterization in Technology, Volume II. Morphological Analysis, CRC Press, Boca Raton, Florida (1984)

[135] Kumar, V., de la Luz Reus-Medina, M., Yang, D., Int. J. Pharm., **235**, 129 (2002)

[136] Yamashiro, M., Yuasa, Y., Kawakita, K., Powder Technol., **34**, 225 (1983)

[137] Carstensen, J. T., Solid Pharmaceutics: Mechanical Properties and Rate Phenomena, Academic Press, London (1980)

[138] **Tüske, Zs**.,Regdon, G. Jr., Erős, I., Srčič, S., Pintye-Hódi, K., **155**, 139 (2005)

[139] Buckton, G., Interfacial Phenomena in Drug Delivery and Targeting, Harwood Academic Publishers, Chur (1995)

[140] **Tüske, Zs**., Erős, I.,Pintye-Hódi, K., Eur. J. Pharm. Sci., **25 Suppl. 1**, S1-S226, P-92 (2005)

[141] Führer, C., Nickel, E., Thiel, F., Acta Pharm. Technol., **21**, 149 (1975)

Acknowledgements

I am very grateful to my supervisor

Professor Dr. Klára Pintye-Hódi

for her support. I greatly appreciate her continuous help during the preparation of my thesis and for providing the excellent facilities for this study. I owe my warm gratitude to her for her criticism, encouragement and numerous discussions during my Ph.D. work.

I would like to thank

Professor Dr. István Erős

Head of the Ph.D. programme Pharmaceutical Technology for providing me with the possibility to complete my work under his guidance.

My warmest thanks go to **Professor Dr. Piroska Szabó-Révész**, present Head of the Department of Pharmaceutical Technology, for her invaluable advice.

I express my grateful thanks to

Professor Dr. Stane Srčič

Head of the Faculity of Pharmacy, University of Ljubljana, for providing the possibility for me to carry out scientific research in his department. I owe him my thanks for his advice and instructions.

I express my kindest thanks to all my co-authors for their collaboration in this work.

I thank all members of the department for their help and friendship.

I owe my thanks to my family, my husband and my friends for their support, encouragement and understanding attitude during these years.