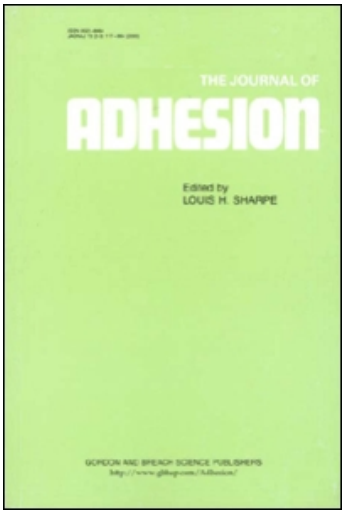

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Effects of the Physicochemical Properties of Metronidazole–Corn Starch Mixtures on the Parameters of the Pellets in the Wet-Granulation Method

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Whether the surface free energy of a powder mixture (metronidazole–corn starch) 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 were investigated. Pellets were produced from the powder mixtures. The interactions between the powder mixtures and the binding agent were first investigated on the basis of the spreading coefficients (S) calculated from the surface free energy. The mechanical properties of the pellets produced were predicted from the S values. Pellet parameters were evaluated as functions of the corn starch content. The overall aim was to investigate the role of the surface free energy of two-component powder compositions in pellet production. In contrast with predictions from the S values, pellets with a more porous and loose texture and with unfavourable mechanical properties can be produced as the S values are increased.

Keywords: Cohesivenes; Mechanical properties; Pellets; Powder mixtures; Surface free energy; Work of adhesion

1. INTRODUCTION

A knowledge of the properties of pharmaceutical solids and excipients is very important in the design of pharmaceutical formulations. One of the most momentous physicochemical parameters of solid materials is the surface free energy (γ_s). This can be estimated directly and indirectly in numerous ways [1–3] and hence, the forces of adhesion

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and cohesion between crystals and particles and also the spreading coefficients (S) can be calculated [4,5]. A knowledge of γ_s is of great significance for an understanding of the interactions between the particles of powders and powder mixtures [4] and the accessories of the equipment [6] in the course of various technological procedures. For this reason, it is important during powder mixing and tabletting. The γ_s data of pharmaceutical powders can be utilized in the formulation of wet-granulation processes to select a suitable binding agent and to predict granule/pellet properties *via* the binder–substrate S values [7–10]. This type of information can also help in the selection of the most suitable coating liquid during film coating [11].

During the design of a solid pharmaceutical formulation from an active agent, it is necessary to know the properties of the materials applied and the interactions between them. In the present work, investigations were made into whether the γ_s value of a powder mixture depends on the proportions of the components and how the forces of cohesion and adhesion between the particles affect the interactions between them as functions of the proportions of the components.

Metronidazole–corn starch powder mixtures were investigated. The typically large metronidazole crystals were not ground or milled to avoid changes in the surface and the physicochemical properties of the particles. Data for γ_s were calculated indirectly through contact-angle measurements with glycerol and diiodomethane, as such measurements were impossible with water because of the resulting disintegration of the compacts containing corn starch.

Pellets were produced from the powder mixtures in a centrifugal granulator, with hydroxypropylcellulose as binding agent. The interactions between the powder mixtures and the binding agent were first investigated on the basis of the S values calculated from γ_s. The mechanical properties of the pellets produced were predicted from the S values. Pellet parameters were evaluated as functions of the corn starch content.

The overall aim of the study was to investigate the role of γ_s in the formation of pellets from two-component powder compositions containing different amounts of a model drug and an excipient. Many factors exert effects. The spreading coefficients S_{12} and S_{21}, the adhesion and cohesion work (W_a and W_c), the particle size, and the amount of the binder are determining features.

2. MATERIALS AND METHODS

2.1. Materials

The model substances used were metronidazole (Ph. Eur. 4th) (length: 194 μm, breadth: 104 μm), corn starch (Ph. Eur.) (12 μm in diameter),

and hydroxypropylcellulose (Klucel LF) (Hercules Inc., Wilmington, DE, USA). The liquids used for contact-angle measurements were glycerol (Riedel-de Haën AG, Seelze, Germany) and diiodomethane (Fluka, Deisenhofen, Germany).

2.2. Methods

2.2.1. Mixing

Powder mixing was performed with a Turbula mixer (Willy A. Bachofen Maschinenfabrik, Basel, Switzerland) (50 rpm for 10 min). The compositions of the powder mixtures prepared are shown in Table 1.

2.2.2. 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, Orpington, 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 Bonaduz, Switzerland). 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. Results for γ_s were calculated from the contact angles at 1 s to avoid the error arising from the drop penetration.

2.2.3. Calculation of Surface Free Energy

In the method of Wu [12,13], γ_s is taken as the sum of dispersive (d) and polar (p) components. The γ_s data 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:

$$(1 + \cos\Theta)\gamma_1 = \frac{4(\gamma_s^d \gamma_l^d)}{\gamma_s^d + \gamma_l^d} + \frac{4(\gamma_s^p \gamma_l^p)}{\gamma_s^p + \gamma_l^p} \quad (1)$$

where Θ is the contact angle, γ_s is the solid surface free energy, and γ_l is the liquid surface tension. The polarity percentage was calculated: $[(\gamma_s^p/\gamma_s) \times 100]$.

TABLE 1 Compositions of the Powder Mixtures

Powder	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

If the γ_s values of the solid materials are known, the S values may be computed, and the interactions between the substrates may be predicted. S is calculated as the difference between W_a and W_c. S for a material spreading over the substrate (S_{12}) and that for the substrate spreading over the material (S_{21}) can be determined according to Eqs. (2) and (3) [7]:

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

$$S_{21} = 4\left(\frac{\gamma_1^d\gamma_2^d}{\gamma_1^d+\gamma_2^d} + \frac{\gamma_1^p\gamma_2^p}{\gamma_1^p+\gamma_2^p} - \frac{\gamma_2}{2}\right) \tag{3}$$

W_c is twice γ_s:

$$W_c = 2\gamma_s. \tag{4}$$

W_a is the energy that arises when two surfaces come into contact:

$$W_a = 4\left(\frac{\gamma_1^d\gamma_2^d}{\gamma_1^d+\gamma_2^d} + \frac{\gamma_1^p\gamma_2^p}{\gamma_1^p+\gamma_2^p}\right). \tag{5}$$

The application of γ_s in the course of wet granulation is described elsewhere [14,15].

2.2.4. Morphological Study

The powder mixtures and the textures of the pellets were investigated with a scanning electron microscope (Hitachi 2400 S, Hitachi Scientific Instruments Ltd., Tokyo, Japan). A polaron sputter coating apparatus (Bio-Rad SC502,VG Microtech, Uckfield, UK) was applied to create electric conductivity on the surface of the samples. The air pressure was 1.3–13.0 mPa.

2.2.5. Cohesiveness

The rearrangement were tested with a Stampvolumeter 2003 (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

$$\frac{N}{C} = \frac{N}{a} + \frac{1}{ab}, \tag{6}$$

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 [16].

2.2.6. Production of Pellets

Pellets containing metronidazole were prepared from powder mixtures of the drug and pharmaceutical additive by using the centrifugal granulator (Freund CF-360, Tokyo, Japan).

The binder solution used in every case was 400 g of a 10% aqueous solution of Klucel LF. The pellets were dried at room temperature ($23 \pm 2^{\circ}C$) for 48 h.

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 size: 0.5 mm in diameter

2.3. Test Methods

Pellets were fractionated on a vibration sieve shaker (Retsch GmbH & Co., Haan, Germany) for 2 min. Size fractions of <315, 315–630, 631–800, 801–1000, and >1000 μm were collected. The investigations were performed with size fraction 801–1000 μm, which accounts for 40–50% of certain pellets.

2.3.1. 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) $\times$ 100]. The measurements were made in triplicate.

2.3.2. Process of Pellet Deformation

The breaking strength and the deformation process were studied with a 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 was measured. The deformation process was used to establish the deformation point. This point is that at which the velocity of force change (N/s) is zero or negative. The breaking force was applied to determine the hardness because the particles investigated were of the same size.

2.3.3. 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 read directly from the cylinder was used to calculate the bulk density according to the mass/volume relationship. 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 three parallel measurements.

2.3.4. Porosity

The porosity of a sample was determined via Eq. (7):

$$\varepsilon = 1 - \frac{\rho_{\text{tap}}}{\rho_{\text{p}}} \times 100 \tag{7}$$

where ε, ρ_{tap}, and ρ_{p} are the porosity, tapped density, and pycnometric density, respectively [17]. 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.

2.3.5. Statistical Evaluation

The mathematical evaluation was carried out with the SPSS for Windows 9.0 package.

3. RESULTS AND DISCUSSION

3.1. Study of Powder Mixtures

The compositions of the powder mixtures prepared are shown in Table 1. The corn starch content of the mixtures was 25, 35, 50, 65 and 75 wt%, respectively.

3.1.1. Contact Angle and Surface Free Energy

The contact angles of the mixtures and of the components were measured in a polar (glycerol) and in an apolar (diiodomethane) liquid.

TABLE 2 Contact Angles, Surface Free Energies, and Polarity Results for Metronidazole, Corn Starch, Klucel LF, and the Powder Mixtures

Sample	Contact angle (°) (SD)		Surface free energy (mN/m)			Polarity (%)
	Glycerol	Diiodomethane	γ_s	γ_s^d	γ_s^p	
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[a]	70.1 (1.5)	28.63 (1.3)	47.9	45.0	2.9	6.1

[a]Klucel LF data were utilized to calculate the S results.

The values of γ_s and S 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 2). 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 [18]. For a powder mixture, γ_s 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 γ_s values of the two components of the mixtures (metronidazole 56.6 mN/m and corn starch 62.3 mN/m) (Table 2), 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%).

3.1.2. Cohesiveness

To obtain additional information, relating to the positions of the particles on the electron micrographs and to explain the slight deviations in the γ_s data, larger masses of the powder mixtures were also investigated. Determination of the rearrangement of powders and powder mixtures provides information on the cohesiveness (and the adhesion properties). The cohesiveness data in Figure 1 demonstrate that the correlation coefficient was more than 0.994 in all cases. 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. The W_a and W_c data are analyzed in detail in Section 3.1.3.

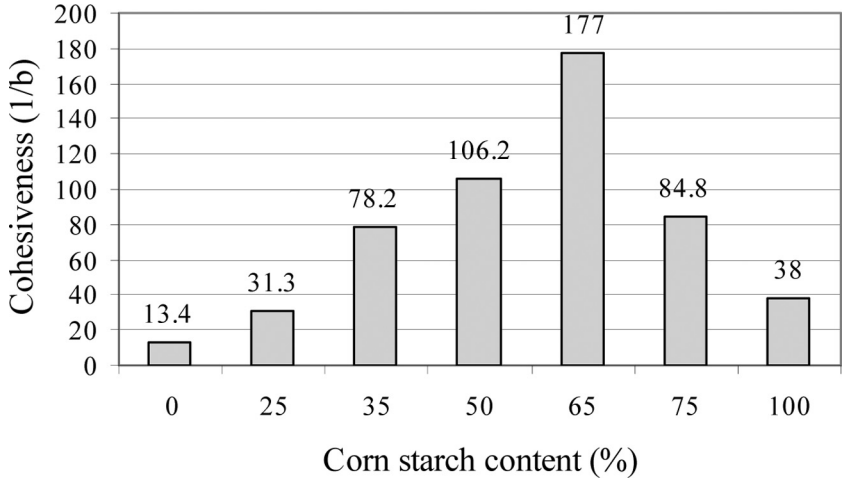

FIGURE 1 Cohesiveness of the samples as a function of the corn starch content ($R > 0.994$).

3.1.3. Scanning Electron Micrographs

The scanning electron micrographs of the mixtures were analysed, and the forces of adhesion and cohesion between the particles were examined. The S_{12} and S_{21} values determined via the 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) [19]. (This phenomenon cannot be visually discerned clearly because of the difference in order of magnitude of the dimensions of the particles: metronidazole: 149 μm, corn starch: 12 μm.) W_a and W_c indicate that the attraction is strongest between the corn starch particles and weakest between the metronidazole crystals (see Table 4). The metronidazole–corn starch W_a is intermediate between the two other data. It is well known from the literature that the W_c between corn starch particles is fairly strong [20].

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) are manifested differently. In Mix25, the relatively small amount of corn starch can be found on the surface of the metronidazole crystals, as a consequence of the adhesion (Figure 2A). In Mix35, the metronidazole crystals are nearly totally covered by one layer of corn starch particles (Figure 2B).

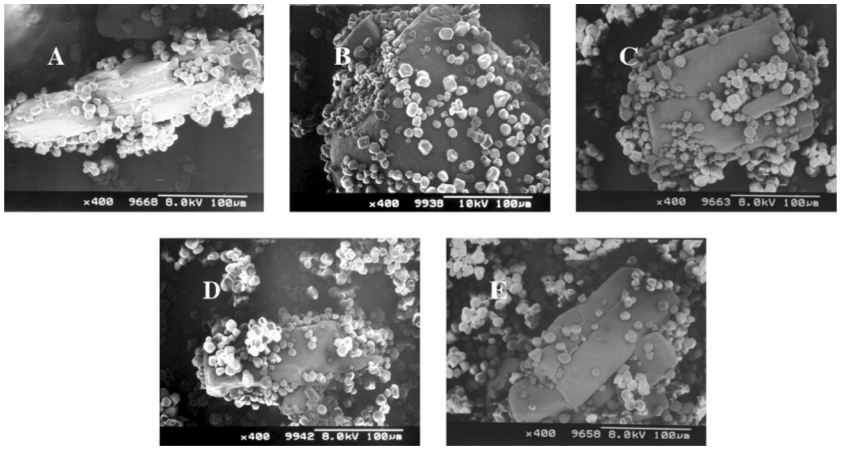

FIGURE 2 SEM micrographs of the powder mixtures: A: Mix25, B: Mix35, C: Mix50, D: Mix65, and E: Mix75.

In Mix50, the corn starch particles are seen mainly on the surface of the metronidazole as a 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 2C). 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 2D). In contrast to 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 2E).

A transition can be observed between Mix50 and Mix65. Accordingly, for a corn starch content of more than 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.

3.1.4. Conclusions

A multisided approach promotes an understanding of why the cohesiveness of Mix65 was so high. The scanning electron micrographs and the cohesiveness results 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 in only 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 plus a relatively large amount of metronidazole: all the corn starch particles are situated on the surface of the metronidazole.
2. More corn starch plus 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 plus a little metronidazole: more corn starch aggregates are formed, due to the relatively 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 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.

3.2. Investigations on Pellets

Pellets were produced from the mixtures investigated in Section 3.1. Connections were sought between the compound of the powder mixtures, the physicochemical 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, similar to the notations of the mixtures.

First, the probable spreading of the binding agent on the surface of the mixtures was investigated. The probable mechanical properties

TABLE 3 Spreading Coefficients of Klucel LF over the Substrates (S_{12}) and of the 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

of the pellets were estimated from the S data. These results can account for the properties of the pellets produced. When the coefficient of spreading of a binder over the substrate (S_{12}) is positive, the formation of dense, nonfriable 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) [9]. When S_{12} is negative and S_{21} is positive, the substrate adheres to the binder at isolated points. In this latter case, the binder solution does not form a film around the powder particles, which leads to the pellets having a more porous, looser texture [4]. The S values for the mixtures, metronidazole, and corn starch are presented in Table 3.

The coefficient of spreading of Klucel LF (1) over the substrate (2) (S_{12}) is positive in every case, whereas that of the substrate over the binder (S_{21}) is negative. Further, 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.

TABLE 4 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	—	

Notes: W_c: work of cohesion; W_a (Metr): work of adhesion between metronidazole and corn starch; and W_a (Klu LF): work of adhesion between binder and substrates.

TABLE 5 Mechanical Properties of the Pellets

Pellet	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 interactions between the particles are influenced by the W_a and W_c; data are given in Table 4.

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 5. 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 friability values of P50 and P65 differed significantly. The friability of the pellets was more significant at a corn starch content of more than 50%.

The bulk and tapped densities of the pellets decreased as the corn starch content was increased (Figure 3). The granules had a looser, more porous structure. An increasing tendency can be detected in the porosity results as the corn starch content was increased (Figure 4). The difference in the porosity of the samples was significant.

Scanning electron micrographs were also prepared for a better understanding of the phenomena. P25 contains 25% corn starch and 75% metronidazole. The pellet texture is dense but slightly porous (Figure 5 A). The scanning electron micrographs reveal that the corn starch particles are enclosed among the larger metronidazole crystals. P35 (Figure 5B) and P50 (Figure 5 C) contain more corn starch than P25. Because of the

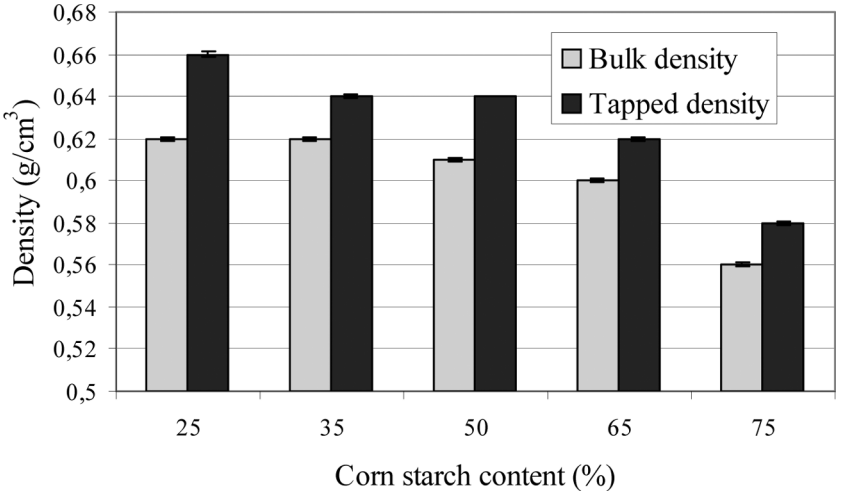

FIGURE 3 Bulk and tapped densities of the pellets.

higher corn starch content, the surface of the metronidazole crystals was extensively covered with small corn starch particles.

P65 (Figure 5D) and P75 (Figure 5E) 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

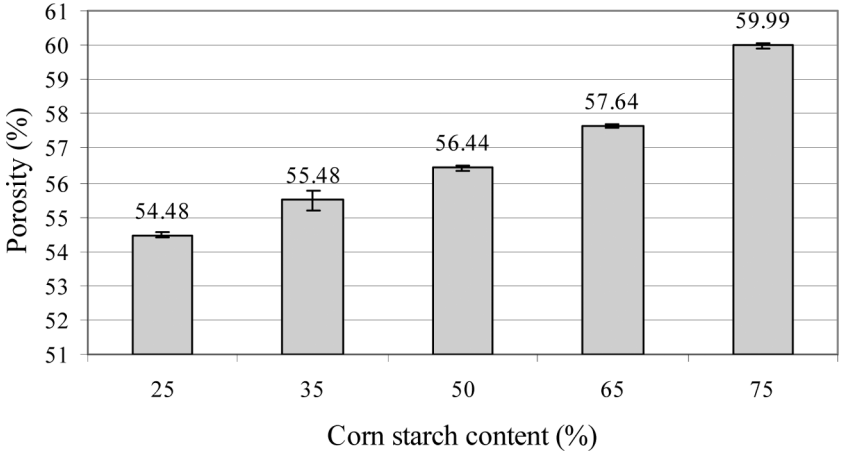

FIGURE 4 Porosity of the pellets.

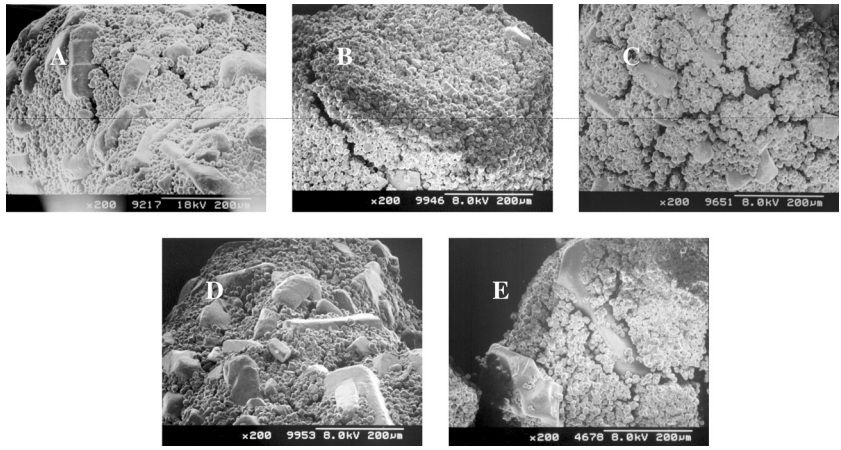

FIGURE 5 SEM micrographs of the pellets: A: P25, B: P35, C: P50, D: P65, and E: P75.

more corn starch. These gaps can be observed on the border of the metronidazole–corn starch aggregates.

The pellet particles 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 Scanning electron microscope 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, similar to that 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 unfavorable.

4. CONCLUSION

The experiments reported here 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 γ_s 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, as the γ_s 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 to 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.

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