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Parya Reisi Nassab^a; Zsófia Tüske^a; Péter Kása Jr.^a; Amir Bashiri-Shahroodi^a; Piroska Szabó-Révész^a

^a Department of Pharmaceutical Technology, University of Szeged, Szeged, Hungary

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Influence of Work of Adhesion on Dissolution Rate in Binary Solid Systems

Parya Reisi Nassab
Zsófia Tüske
Péter Kása Jr.
Amir Bashiri-Shahroodi
Piroska Szabó-Révész

Department of Pharmaceutical Technology, University of Szeged,
Szeged, Hungary

In powder mixtures, the interactions between the particles are determined by the forces of adhesion and cohesion. The size and the specific surface area of the particles are also determinative factors in the interparticle interactions.

The aim of the present work was to investigate the surface properties of different physical mixtures of meloxicam (ME) and find a possible relation between surface properties and dissolution of physical mixtures. The contact angle, surface free energy, polarity, work of adhesion, and work of cohesion of the drug, the carrier, and their physical mixtures were calculated.

ME samples with different particle sizes were investigated without the carrier and in two different ratios with mannitol. A smaller (micronized) particle size without the carrier did not improve the dissolution of the drug. However, with the ideal particle size of the drug (ME₂) and the ideal ratio of ME and mannitol (1:10), total dissolution of drug was achieved. In this case, mannitol functioned as a core covered with a monolayer of ME particles. The contact angle, the surface free energy, the polarity, and the work of adhesion can be used as critical parameters to characterization of a powder mixtures and determination of optimum dissolution profile.

Keywords: Contact angle; Dissolution rate; Mannitol; Meloxicam; Spreading coefficient; Work of adhesion

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Address correspondence to Piroska Szabó-Révész, Department of Pharmaceutical Technology, University of Szeged, Eötvös u. 6., H-6720, Szeged, Hungary. E-mail: revesz@pharm.u-szeged.hu

1. INTRODUCTION

Surface free energy is one of the most useful physicochemical parameters of solid materials (powders) which can be used to design a pharmaceutical formulation. Information about contact angle and surface free energy is helpful to estimate the interactions between the particles in powders (powder mixtures). Additionally, in powder mixtures, the interactions between the particles are determined by the forces of adhesion and cohesion [1].

Surface free energy is among factors (roughness or contact area, hardness, particle size and shape, and surface free energy) that influence particle adhesion, but adhesion between powder particles of different materials during mixing will only occur if the energy that is released during the adhesion of the particles is larger than the energy that is required to break up an autoadhesion (cohesion interaction) [2].

The rate of dissolution of a drug with poor solubility in water depends among other factors on the effective surface area, the wettability, and the energy state of the crystals of the active agent. Numerous formulation techniques may be used to improve the dissolution and bioavailability of practically insoluble drugs, *e.g.* melt technologies [3,4], solvent evaporation [5], particle size reduction by supercritical fluid processes [6], and spray drying or the preparation of binary physical mixtures (PMs) using different carriers [7]. Use of a carrier is one of the easiest strategies to improve the dissolution [8].

Meloxicam (ME) is one of the new non-steroidal anti-inflammatory drugs (NSAIDs), a potent inhibitor of cyclooxygenase, and in several models exhibits selectivity for the inducible isoenzyme cyclooxygenase-2 [9]. This characterization has led to ME being used as a good medication in the therapy of chronic osteoarthritis and rheumatoid arthritis [10]. ME is practically insoluble in water and it can be categorized in Class II of the Biopharmaceutical Classification System [11].

β -D-mannitol was chosen to serve as a carrier. Mannitol is a sugar alcohol with a sweet taste but a low calorie content, which is widely used in the pharmaceutical and food industries [12]. In this work, the aim was to find a connection between the surface properties of the samples (wettability, surface energy, polarity, and work of adhesion) and the rate of dissolution. Three MEs were used, with different particle sizes:

- ME1: with the largest particle size and the smallest surface area,
- ME2: ground ME1, and
- ME3: micronized ME, with the smallest particle size.

2. MATERIALS AND METHODS

2.1. Materials

ME samples with different particle sizes (ME1 and ME3) were supplied by EGIS, Ltd. (Budapest, Hungary). ME2 was made by the milling of ME1 with a ball mill (PM200 Retsch GmbH & Co. KG, Haan, Germany) at 400 rpm for 30 min. β -D-Mannitol was from Hungaropharma, Ltd. (Budapest, Hungary). The structures of the ME and mannitol as carrier are shown in Fig. 1.

The particle sizes and specific surface areas of the MEs and the mannitol were measured by laser diffraction (Malvern Mastersizer 2000, Malvern, Ltd., Worcestershire, UK). For the measurements, the materials were dispersed with air and deagglomerated at an air pressure of 0.5 bar. The particle size was determined in the range 0.02–2000 μm . The specific surfaces of the samples were calculated from the particle size data. The measurements were repeated three times (Table 1).

2.2. Methods

2.2.1. Contact Angle Measurements

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, Kent, UK) with a 20 s dwell time at a pressure of 4×10^8 Pa. The contact angle (θ) 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, Hamilton Bouaduz AG, Bouaduz, Switzerland). Photos were taken with a video camera every second up to 10 s from coming into contact of the drop with the compact. The contact angles

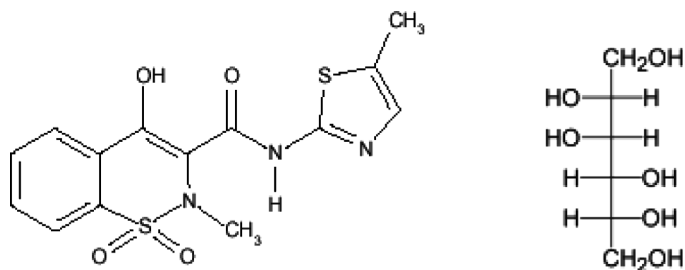


FIGURE 1 Structures of meloxicam and mannitol.

TABLE 1 Particle Sizes and Specific Surface Areas of the Materials

Material	d(10%) μm	d(50%) μm	d(90%) μm	Specific surface area (m^2/g)
ME1	50.50	106.66	206.20	0.07
ME2	1.62	25.74	131.15	1.37
ME3	0.72	2.49	5.97	2.51
Mannitol	17.61	86.74	239.45	0.23

were calculated from the contours of the drop. The solid surface free energy (γ_s) results were calculated from the contact angles at 1 s to avoid the error arising from the drop penetration.

2.2.2. Calculation of Surface Free Energy (γ_s), Spreading Coefficient (S), Cohesion (W_c) and Works of Adhesion (W_a)

Different methods for surface energy assessment are available [13]. The traditional method is to measure a liquid contact angle on solid samples. Contact angles have to be measured with several liquids to assess the surface free energy of a powder. In the method of Wu [14] two liquids of known polar (γ_l^p) and dispersion (γ_l^d) components are used for measurement. The solid surface free energy is the sum of polar (γ_s^p) and nonpolar (γ_s^d) components and is calculated according to Eq. (1):

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

where θ is the contact angle, γ_s is the solid surface free energy and γ_l is the liquid surface tension.

For the two component approach (Wu's method), a combination of water and diiodomethane, the polar and nonpolar liquids with the highest possible surface tension, exerts minimum influence on the result. The liquids used for contact angle measurement were bidistilled water ($\gamma^p = 50.2 \text{ mN/m}$, $\gamma^d = 21.8 \text{ mN/m}$) and diiodomethane ($\gamma^p = 0 \text{ mN/m}$, $\gamma^d = 50.8 \text{ mN/m}$). The polarity percentage was calculated from γ_s^p and γ_s values: $(\gamma_s^p/\gamma_s) \times 100$.

If the γ_s values of the solid materials are known, the spreading coefficient (S) values may be computed and the interactions between the substrates may be predicted. S is calculated as the difference between works of adhesion (W_a) and cohesion (W_c). S for a material (ME1, ME2, ME3) spreading over the other material (mannitol) (S_{12}) and that for the second material spreading over the first material (S_{21}) can be

determined according to Eqs. (2) and (3) [15]:

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

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

When the ME spreads over the mannitol, the spreading coefficient (S_{12}) is positive. This value is negative (S_{21}) when the mannitol is over ME crystals.

W_c is twice γ_s , since two identical surfaces interact:

$$W_c = 2\gamma_s. \quad (4)$$

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

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

2.2.3. Preparation of PMs

PMs of ME1, ME2, and ME3 with mannitol (PM1, PM2 and PM3) in (drug:carrier) ratios of 3:7 and 1:10 were obtained by mixing the individual components for 10 min in a Turbula mixer (Turbula WAB, Systems Schatz, Basel, Switzerland) at 50 rpm. For the development of the ratios of the components of the PMs, the starting point was the particle sizes and the specific surface areas of the components (ME1, ME2, ME3, and mannitol) [16].

2.2.4. Morphological Study

The binary systems were investigated with a scanning electron microscope (Hitachi 2004 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. Dissolution Studies

PMs of 15 mg of ME and the appropriate amount of mannitol were filled into hard gelatine capsules [6]. Dissolution tests were performed by using Pharmatest equipment (Hainburg, Germany) at a paddle speed of 100 rpm; 900 ml of phosphate buffer pH 7.5 (± 0.1) (Ph.Eur.4) at 37°C ($\pm 0.5^\circ\text{C}$) was used. The ME contents of the samples were measured spectrophotometrically at 362 nm (Helios α Spectronic,

Unicam, Cambridge, UK). The dissolution experiments were conducted in triplicate.

3. RESULTS AND DISCUSSION

3.1. Study of Pure Materials

First, the surface properties of the MEs and mannitol were investigated. The data of contact angles in Table 2 reveal that the ME samples have medium wettability ($\theta_{water} = 54.4\text{--}69.4^\circ$). Mannitol as a water soluble carrier possesses very good wettability ($\theta_{water} = 24^\circ$). The wettability of the MEs is in every case lower than that of mannitol. The total surface free energies of the pure MEs are lower than that of mannitol. The polarity of surfaces, which is connected with the surface free energy, decreases with reduction of particle sizes of MEs, consequently, with increases in the hydrophobic surface area. The work of cohesion and the work of adhesion yield appreciable information on the interactions between the particles (Table 2).

The work of cohesion of the ME samples is in every case lower than that of mannitol. This is necessary for the spreading of the ME over the mannitol. The work of adhesion between the mannitol and ME samples is in every case higher than the work of cohesion of the corresponding ME samples. This is also a necessary condition for the spreading of the active agent on the surface of the excipient (Table 3). It is interesting that the works of cohesion and adhesion are lower for ME3 than that for ME1 and ME2 and the spreading coefficient of the ME3 over mannitol (S_{12}) is between the spreading coefficients of ME1 and ME2. As we assessed in our previous work [16], these conditions are necessary for the spreading of one component over the surface of the other, though the particle size and the proportions of the components can modify the arrangement of the particles under different conditions.

TABLE 2 Surface Properties Data of the Pure Components

Samples	Contact angle ($^\circ$)		Surface free energy (mN/m)	Polarity (%)	Work of cohesion (mN/m)	Work of adhesion (mN/m)
	Water	SD (\pm)				
ME1	54.4	2.4	67.9	27.8	135.8	144.7
ME2	59.9	1.2	65.9	24.4	131.8	140.7
ME3	69.4	3.7	59.2	19.4	118.3	129.5
Mannitol	24.0	4.5	80.6	40.7	161.2	–

TABLE 3 Spreading Coefficients of the MEs Over Carrier (Mannitol) (S_{12}) and of the Mannitol Over the MEs (S_{21})

1	2	mN/m	
		S_{12}	S_{21}
ME1	Mannitol	7.9	-20.4
ME2	Mannitol	9.6	-26.7
ME3	Mannitol	8.8	-20.7

The dissolution rates of the pure MEs (without mannitol) with different particle sizes were studied (Fig. 2). The dissolution of the pure MEs was slow because of the low polarity values. On decrease of the particle size, the dissolution rate for ME2 increased, but a small particle size was not sufficient to achieve a dissolution rate of 40% in 90 min. Although the particles of ME3 were the smallest, these particles tended to agglomerate, and accordingly the dissolution was decreased as compared with ME1.

3.2. Study of Physical Mixtures

The contact angles of the PMs are between those of the ME and mannitol (Table 4). Interestingly, a difference may be observed between the PM1 group and the PM2 and PM3 groups. The θ_{water} values for the latter (PM2 and PM3) are closer to the contact angle of the ME than to that of mannitol. This phenomenon is more marked at a ratio

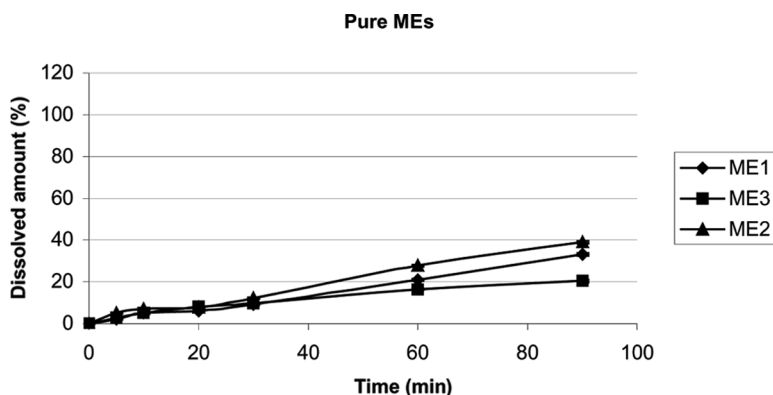
**FIGURE 2** Rates of dissolution of pure MEs with different particle sizes.

TABLE 4 Surface Properties Data of ME-Mannitol PMs in a Ratio 3:7

Samples	Contact angle (°)		Surface free energy (mN/m)	Polarity (%)
	Water	SD (\pm)		
PM1-3:7	38.2	2.4	75.3	35.6
PM2-3:7	57.9	1.8	66.9	25.9
PM3-3:7	60.3	1.6	63.5	24.7

of 3:7. This presumably means that at this ratio the ME is spread over the surface of the mannitol, whereas at a ratio of 1:10 the ME does not totally cover the mannitol (Table 5). In the PM1 group, the two different particles are side by side, so the good wettability of mannitol can be observed.

The same tendency can be seen in the surface free energies of the PMs as in the contact angles in accord with the presumed positions of the two different particles. Consequently, the surface free energy and polarity data on the PM1s were closer to those on mannitol than to those on ME1. For the PM2s and PM3s, the coverage of the mannitol by the ME results in the surface free energies approximating to those for the pure MEs.

Through the use of PMs in a ratio of 3:7, the dissolution was improved in every case as compared with the dissolution of the pure MEs; a maximum of 80% dissolution was achieved from the PM2 sample (Fig. 3). For PM1, because of the large particle size of both mannitol and the ME, the particles remained side by side. The amount of drug dissolved after 90 min was only 40%. In the case of PM3, ME particles spread over the surface of the mannitol particles but, because of their tendency to agglomerate, the dissolution rate was only slightly improved. Even though the particles of the ground ME1 (ME2) were not as small as those of ME3, it was able to achieve a higher surface area in contact with the dissolution medium. The highest dissolved amount and a faster dissolution of the drug were detected here.

TABLE 5 Surface Properties Data of ME-Mannitol PMs in a Ratio 1:10

Samples	Contact angle (°)		Surface free energy (mN/m)	Polarity (%)
	Water	SD (\pm)		
PM1-1:10	31.4	2.1	77.9	38.4
PM2-1:10	42.8	4.9	73.9	32.9
PM3-1:10	54.4	1.2	66.4	27.8

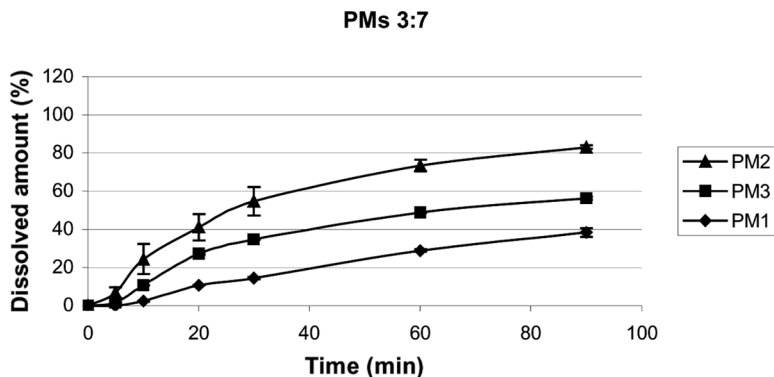


FIGURE 3 Rates of dissolution of ME-mannitol PMs in a ratio of 3:7.

Through the use of PMs in a ratio of 1:10 the dissolution was improved for PM2 and PM3 as compared with the dissolution of the pure MEs. For PM1, the amount of drug dissolved did not differ from that of the pure ME1. The dissolution profile of PM1 with a ratio of 1:10 differed from those of PM2 and PM3 (Fig. 4).

Because of the large particles of both mannitol and the ME (PM1), the particles remained side by side. The amount of drug dissolved was not improved as compared with ME1. In the case of PM3, the ME particles spread over the surface of the mannitol particles, but because of their tendency to agglomerate, the amount dissolved was improved to only 80%. As compared with PM3 in a ratio of 3:7, the amount dissolved here was much higher because of the larger amount of mannitol and, therefore, the larger surface area. Although ME3 tended to agglomerate, the proportion of agglomerates was lower and, thus, fas-

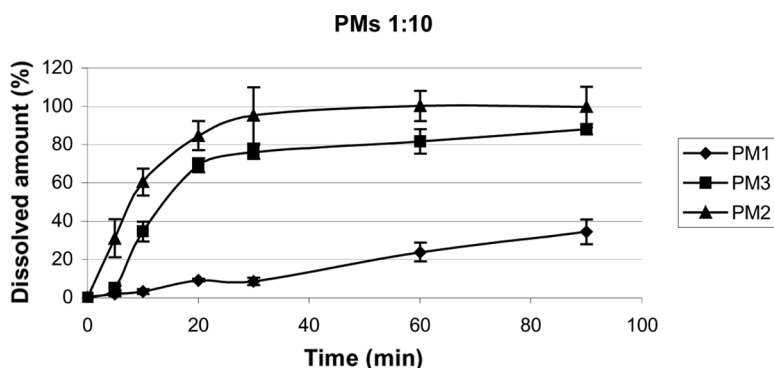


FIGURE 4 Rates of dissolution of ME-mannitol PMs in a ratio of 1:10.

ter drug dissolution was achieved. Even though the particles of the ground ME1 (ME2) were not as small as those of ME3, it was able to attain a higher surface area in contact with the dissolution medium and the dissolved amount was improved to 100%. A monolayer coverage of mannitol was reached.

Establishment of the ideal ratio meant not only that the maximal dissolution was approached, but also the rate of dissolution of the ME (with appropriate particle size) was improved so that almost the whole PM2 was dissolved by 40 min. Such an improvement occurred only in the case of MEs with small particle sizes. Small ME particles spread over the surface of the mannitol. Through the improvement of the content of smaller particles in the binary mixtures, the cohesion between the ME particles was increasingly pronounced. From this aspect, the dissolution of PMs with a ratio of 3:7 was unfavourable.

3.3. Morphological Study of Physical Mixtures

The scanning electron micrographs support the conclusions drawn from the wettability measurements and the investigations of the inter-particle interactions (Fig. 5).

Two groups may be distinguished:

- PM1s: The mannitol and ME particles are in close proximity because of the large particle size of ME1, which is close to that of mannitol; only a small particle fraction of ME1 can adhere to the surface of the mannitol.

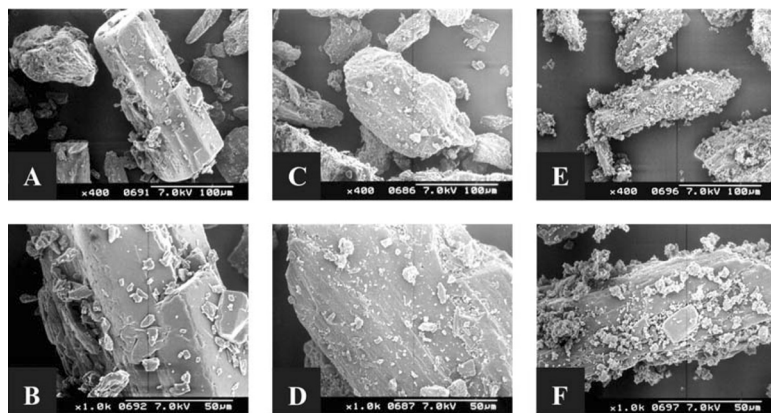


FIGURE 5 SEM micrographs of PMs 1:10—A, B: PM1; C, D: PM2; E, F: PM3.

- PM2s and PM3s: ME2 and ME3 have smaller particle sizes than those of mannitol. After mixing, therefore, each particle of mannitol will be a core surrounded by small particles of MEs. For PM3, the micronized ME3 is spread over the surface of the carrier, but tends to agglomerate because of the small particle size and the higher specific surface area. For PM2, the situation is the same, except for the tendency to agglomerate. In the case of PM3 the proportion of smaller ME particles is higher, and the coverage of the mannitol crystals is more significant (see θ and γ for the mixtures), but the ME2 particles compose agglomerates.

From the contact angle, the surface free energy, the polarity, and the W_a and W_c data supplemented with the morphological study of the PMs, the optimum dissolution profile was expected for the PMs with ME2. For the small, but not micronized crystals, monolayer coverage of the mannitol was attained.

4. CONCLUSIONS

Preparation of a PM is one of the easiest ways to increase the dissolution of insoluble drugs, but it is sometimes not effective enough to be used by researchers. Through the establishment of an ideal ratio for the binary system and an appropriate particle size for the ME, use of a PM can be as effective as any other method, involving, for example, a eutectic mixture or complexation.

As demonstrated earlier, the interparticle interactions in two-component mixtures are influenced extensively by the particle size and the proportions of the components. The present results show that this phenomenon may be applied for dissolution improvement. With the ideal particle size and ideal proportions of the carrier and drug, the interparticle interactions are optimally influenced by the surface properties and particle size. Of the binary mixtures applied here, PM2 with a ratio of 1:10 proved ideal for 100% dissolution of the drug to be attained within 90 min. The dissolution of the drug from binary mixtures could be predicted from the surface properties and morphological study of the PMs.

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