Influence of the organization of binary mixes on their compactibility

Barra, Jérôme; Falson-Rieg, Françoise; Doelker, Eric

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J. Barra,[1,2,4] F. Falson-Rieg,[3] and E. Doelker[1]

Received May 21, 1999; accepted June 14, 1999

Purpose. Elucidate the compactibility of binary mixes from their organization as compared to the traditional approach involving the different behavior of the materials under compression (plastic or brittle).

Methods. Several materials were selected from their surface energies. Binary mixes 50/50 v/v were prepared from different sieved or freeze-milled fractions. The tensile strengths of the tablets obtained at two compression forces were compared with those of series of compacted binary mixes containing different proportions of the raw materials (concept of equivalent media).

Results. In the case of interacting mixes, when the differences in particle size between the fractions blended increased, the material with the lowest particle size coated the largest particles more efficiently. Consequently, the tensile strengths of the tablets obtained became closer to the tensile strengths obtained from the pure coating material. For the non-interacting systems, the experimental tensile strengths were very close to the values calculated from the tensile strengths of the pure materials.

Conclusions. This study clearly demonstrates the influence of the organization of binary mixes on their compactibility. The adhering material makes a percolating network governing the tensile strength of the tablet. From an industrial point of view, it is possible to improve the compactibility of binary mixes without changing their composition by selecting the appropriate organization.

KEY WORDS: powder; binary mixes; compactibility; surface energy; particle size; tensile strength.

INTRODUCTION

Drugs are often characterized by a low water solubility and exhibit a poor compactibility. To solve these problems, solid dosage formulations include several excipients such as binders, diluents, and disintegrants. However, if the dosage form contains a relatively high percentage of active ingredient, poor compactibility may become a problem. The aim of this study is to provide a method for changing the compactibility of a mix, defined as the ability of a powdered material to be compressed into a tablet of a specified strength (1), without changing its composition.

In a recent publication (2), we isolated sieved fractions of different sizes of two active ingredients (niflumic acid NA and ibuprofen Ibu) and two excipients (ethyl cellulose EC, hydroxypropyl methylcellulose HPMC). After blending the fractions together, the resulting interactions were evaluated by scanning electron microscopy and related to two physical parameters: surface energy and particle size. This previous study demonstrated that binary mixes of identical composition could have different organizations, depending on the surface energy and particle size of the fractions used. In the present study, we determined the influence of these different organizations on the compactibility of the mixtures. We selected the two mixes with the most interaction (NA/EC, NA/HPMC) and the mix with the least interaction (EC/HPMC). We added a fourth interactive mix to increase the number of examples (niflumic acid with a low substituted hydroxypropyl cellulose L-HPC) and to provide an intermediate interacting system.

MATERIALS AND METHODS

Materials

Analytical grades of diethylene glycol, 2-aminoethanol, diiodomethane, and aniline were purchased from Sigma (Buchs, Switzerland) to determine the surface energies of the constituents: niflumic acid (Hexachimie, Agen, France), ethyl cellulose 10 mPa.s (Dow Europe, Horgen, Switzerland), hydroxypropyl methylcellulose USP type 2910 (Shin Etsu, Tokyo, Japan), and low substituted hydroxypropyl cellulose (Shin Etsu, Tokyo, Japan). All materials were kindly supplied by UPSA, Agen, France. The ethyl cellulose 10 mPa.s grade was selected because it was previously found to have the highest compactibility among the 10, 20, 45, and 100 mPa.s grades (3).

Preparation of the Binary Mixes

Four series of binary mixes were prepared: niflumic acid with ethyl cellulose, niflumic acid with hydroxypropyl methylcellulose, niflumic acid with a low substituted hydroxypropyl cellulose; and ethyl cellulose with hydroxypropyl methylcellulose. Blends were made from the powders as received or after sieving with an Alpine air-jet sieve (Augsburg, Germany) equipped with 20, 32, 45, 63, and 125 μm sieves (Fritsch GmbH, Idar-Oberstein, Germany) or after milling with a Spex 6700 freezer mill (Industries Inc., Edison, NJ, USA). The particle size of the raw materials and of the milled fractions were determined with a Malvern Mastersizer S long bench (Malvern, UK).

Using a Turbula (Basel, Switzerland) blender, identical true volumes of each powder were blended for 20 min in a 25-mL cylindrical glass container, filled to 14 mL (56%), to ensure optimum blending. To obtain identical real volumes, the true density (ρ) of each powder (A or B) and the bulk density (D) of each particle size fraction were needed (Table I). These densities were determined with a Beckman (Irvine, California, USA) air comparison pycnometer model 930 and a 20-mL

[1] School of Pharmacy, University of Geneva, Quai Ernest-Ansermet 30, 1211 Geneva 4, Switzerland.
[2] Laboratoires UPSA, 128, rue Danton, BP 325, 92506 Rueil-Malmaison, France.
[3] Faculty of Pharmacy, Claude Bernard University, 8 avenue Rockefeller, 69008 Lyon, France.
[4] To whom correspondence should be addressed. (e-mail: jerome.barra@pharm.unige.ch)

0724-8741/99/0900-1449$16.00/0

Table I. Particle Size, Apparent and True Densities of Niflumic Acid (NA), Ethyl Cellulose (EC), Hydroxypropyl Methylcellulose (HPMC) and Low Substituted Hydroxypropyl Cellulose (L-HPC)

	NA	EC	HPMC	L-HPC
	Mean particle size (μm)			
Raw material	9.9	90.0	28.9	16.2
	True density ($g.mL^{-1}$)			
Raw material	1.56	1.27	1.36	1.48
	Apparent density ($g.mL^{-1}$)			
Raw material	0.74	0.46	0.38	0.38
63–125 μm	0.59	0.35	0.32	0.47
45–63 μm	0.66	0.35	0.31	0.36
32–45 μm	0.63	0.33	0.29	0.31
20–32 μm	0.53	0.30	0.31	0.32

volumetric flask. Then, the following equations were used to determine the weight (w) of each fraction:

$$w_A = \frac{14.D_A.D_B.\rho_A}{D_B.\rho_A + D_A.\rho_B} \quad (1a)$$

$$w_B = \frac{14.D_A.D_B.\rho_B}{D_B.\rho_A + D_A.\rho_B} \quad (1b)$$

Determination of Surface Energies

The method used was the same as described by Barra *et al.* (2). The surface energies of the pure materials are given in Table II. The absolute difference between the two spreading coefficients ${}^{B/A}\lambda$ and ${}^{A/B}\lambda$ is a valuable estimate of the potentiality of interaction between the particles blended (2). Its value for all the mixes studied is presented in Table II.

Evaluation of the Organization of the Binary Mixes

Scanning Electron Microscopy

Samples were mounted directly onto a SEM sample stub using a double-sided adhesive carbon layer and coated with a 150 Å thick gold film under reduced pressure (Balzers Sputter Coater SCD004, Balzers, Principality of Liechtenstein). The organization of the mixes could be inferred from photographs taken using a Jeol scanning electron microscope 6400 (Tokyo, Japan) at magnifications of ×100 and ×500.

Table II. Surface Energy of the Pure Materials and the Parameter $|{}^{B/A}\lambda - {}^{A/B}\lambda|$ of Each Blend as Defined in (2)

	Surface energy of the first material of each series ($mN.m^{-1}$)			$\lvert{}^{B/A}\lambda - {}^{A/B}\lambda\rvert$ $N.m^{-1}$
	γ_d	γ_p	γ	
NA/HPMC	26.2	19.7	45.9	21.8
EC/NA	25.0	10.8	35.8	20.2
L-HPC/NA	20.1	18.6	38.7	14.4
HPMC/EC	21.7	13.3	35.0	3.7

Notion of Equivalent Media

Another method for evaluating the organization of the binary mixes is to compact them and compare the tensile strengths of the tablets obtained. However, when comparing the tensile strength of two mixes, and finding a mix that has a tensile strength 30% higher than another mix, the tensile strength cannot be used to assess reliably the influence of the organization on the compactibility of the materials. Such an increase of the tensile strength may come from: (i) a different organization of the mixes; (ii) a different consolidation mechanism of the two materials; or (iii) a different compactibility of the fractions used, since usually the compactibility increases with decreasing particle size. Thus, it may be difficult to compare the tensile strength of two mixes, if the Patter contain different particle size fractions of materials with different consolidation mechanisms. To avoid this problem, we decided to compare each of the mixes to the same standard (a kind of calibration curve transposed to the solid state), as usually done when dosing the blood concentration of a drug by spectrophotometry when comparing the absorbance of the sample to the absorbance of standards. Thus, a mix containing 50/50 v/v sieved fractions of materials A and B will behave as a mix of the two raw (unsieved or unmilled) materials containing x% of material A. A series of binary mixes containing different proportions of each raw components was prepared (0/100, 12.5/87.5, 25/75, 37.5/62.5, 50/50, 62.5/37.5, 75/25, 87.5/12.5, 100/0). The tensile strengths of the compacts obtained were used to make the calibration curve for each mix. If the organization of the binary mix has an influence on the compactibility of a mixture, then different mixes with different organizations, but identical composition should behave differently. To determine the extent of the difference between the compactibility of binary mixes, their tensile strengths were reported on the calibration curve, to determine the equivalent media, i.e. which proportion of NA in the case of NA/EC, NA/HPMC, and NA/L-HPC and EC in the case EC/HPMC gives tablets with an identical tensile strength. These values were then used to compare the different mixes.

Preparation of the Compacts

Powder sufficient to produce a 2-mm high tablet at zero theoretical porosity was manually introduced into a 12-mm diameter die cavity. The powder bed was then compressed at two forces (9.3 and 44.0 kN) for 15 seconds using a Specac hydraulic press (Sidcup, England).

Compact Strength

The load P required to diametrically fracture the tablets was applied using a Schenk-Trebel RM 50 mechanical testing machine (Ratingen, Germany) at a cross-head speed of 3 mm/min, equipped with a load-sensitive cell (HBM Z3H2, Hottinger Baldwin Messtechnik, Darmstadt, Germany). This value was then used to calculate the tensile strength (σ) immediately after ejection of the compact (4):

$$\sigma = \frac{2.P}{\pi.D.h} \quad (2)$$

where D is the compact diameter, and h its thickness.

RESULTS AND DISCUSSION

Compactibility of Pure Materials Without Sieving, and Their Mixes

To assess the effect of the organization of the binary mixes on their compactibility, it was first necessary to study the compactibility of the pure materials. As illustrated in Fig. 1a, niflumic acid is a poorly compactible material, whereas EC, HPMC, and L-HPC have good compactibilities. The compactibility of NA is always improved when blended with EC, HPMC, or L-HPC (Fig. 1b). Note, the improvement is higher with L-HPC and HPMC than with EC. This observation will be discussed later.

After these first experiments, we decided to study the compactibility of the binary mixes obtained from the sieved and freeze-milled fractions at low and high compression forces. Thus, two different domains of consolidation could be studied where the relative importance of particle fragmentation and plastic deformation could differ. The compression forces selected for this study were 9.3 kN and 44.0 kN. Results were similar at both compression forces. Here, only those results obtained at 44.0 kN are presented and discussed.

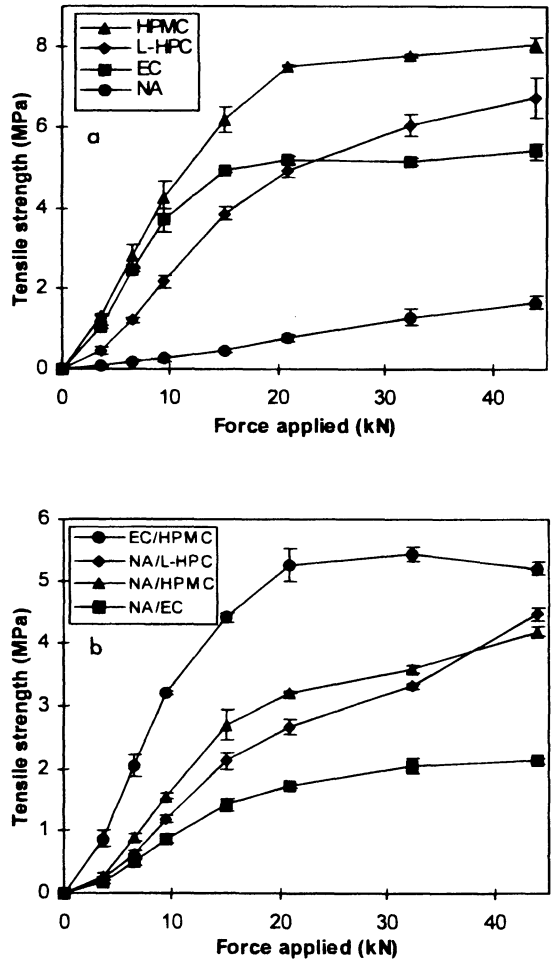

Fig. 1. Tensile strengths of compacts of pure NA, EC, HPMC and L-HPC (a) and of their 50/50 v/v mixes (b) obtained at different compression forces. When error bars are not visible, they are included within the size of the symbols.

Equivalent Media

Figure 2 presents the different calibration curves and their equations, obtained with all the series (NA/EC, NA/HPMC, NA/L-HPC, and EC/HPMC). Interestingly, the tensile strength of the tablets obtained is linearly related to the composition of the mixes for the NA/HPMC and NA/L-HPC series. Fell and Newton (4) observed linear relationships between the tensile strength of tablets prepared from α-anhydrous and β-anhydrous lactose binary mixes of approximately similar particle size at 20 kN compaction load, and their composition. They used this relationship to predict the tensile strength of binary mixtures. The compactibility of aspirin-caffeine and aspirin-metamizol mixes was also found to be linearly related to the relative proportion of the two components, thus indicating no interaction (5).

The lower tensile strengths obtained with the NA/EC and EC/HPMC series, when compared to linear relationships, indicate that NA, EC, and HPMC particles preferentially bind with each other, instead of bonding with the other material of the mix. This suggests the adhesion bonds are weaker than the cohesion bonds between each material. This has been observed previously for anhydrous lactose-sucrose (1), anhydrous lactose-Avicel PH-102 (6), KCl-Avicel PH-102 (7), caffeine-magnesium stearate (8), and caffeine-sodium lauryl sulphate (8) mixtures. The negative effect on the tensile strength was attributed to the predominance of cohesive attraction over the adhesion attraction. In contrast, marked peaks in the tensile strength-composition curves for tablets compacted from mixes of aspirin-Emcompress (9), phenacetin-Emcompress (10), Emcompress with KCl, boric acid, aspirin, or PEG 4000 (7) indicated higher adhesion bonds between the components than their cohesion bonds. In a recent study on the effect of composition on the tabletting indices of binary powders mixtures, Majuru and Wurster (11) concluded that it is possible to predict the bonding indices when the mechanisms of consolidation of the components are known. Linear relationships were observed between the tableting indices of several binary mixtures when the materials blended had the same consolidation mechanisms (plastic

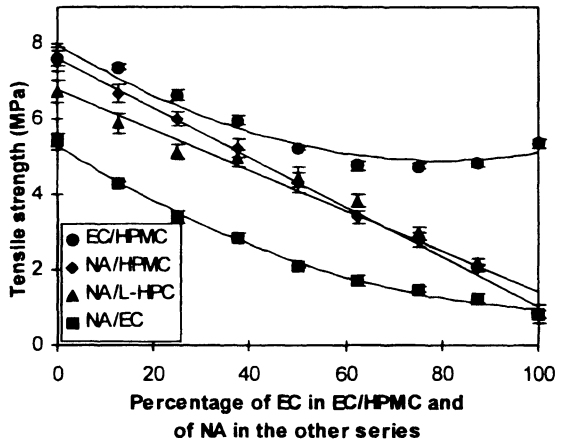

Fig. 2. Tensile strength of compacts obtained at 44.0 kN containing different proportions of ethyl cellulose or niflumic acid in the EC/HPMC ($y = 0.0005x^2 - 0.0780x + 8.0088$), NA/HPMC ($y = -0.0658x + 7.6190$), NA/L-HPC ($y = -0.0537x + 6.8000$) and NA/EC ($y = 0.0004x^2 - 0.0807x + 5.3093$) series. When error bars are not visible, they are included within the size of the symbols.

materials: pregelatinized corn starch, anhydrous theophylline, and Avicel PH-101, or brittle materials: anhydrous lactose, sodium sulfathiazole, and mannitol), whereas second-degree polynomial equations were observed when a brittle material was blended with a material undergoing plastic deformation.

Sometimes, the relationship between the composition of a binary mix and the tensile strength of the compact is not obvious. Riepma *et al.* (12) studied the compression of binary mixes of different types of crystalline lactose. They showed a non-proportional inter-correlation between the tablet strength and the composition of the powder mixes, even though all the types of crystalline lactose had a similar consolidation mechanism. The strength of tablets prepared from mixes of Emcompress and phenacetin was not a simple function (linear or quadratic) of the strength of the tablets of the individual components (10). However, a linear relationship between the logarithm of the applied pressure and the porosity of the tablets was found. The authors concluded that it was not possible to predict the tensile strength of tablets prepared from mixing of materials consolidating by different mechanisms.

Blends of Niflumic Acid with Ethyl Cellulose

The sixteen binary mixes of each series (NA/EC, NA/HPMC, NA/L-HPC, EC/HPMC) prepared from different sieved fractions ([63–125 μm], [45–63 μm], [32–45 μm], and [20–32 μm]) were compacted at 9.3 and 44.0 kN. The particle size distribution within each class was assumed to be uniform or of a Gaussian-type, so the mean particle sizes of each fraction were estimated to be 94, 54, 38.5, and 26 μm, respectively. The apparent percentages of niflumic acid in the mix were calculated from the experimental tensile strengths obtained with the 50/50 v/v binary mixtures of raw materials. The apparent percentages versus the mean particle size difference between NA and EC are presented in Fig. 3 at 44.0 kN (a). For example, when a [63–125 μm] sieved fraction of NA is blended with a [45–63 μm] sieved fraction of EC, the mean particle size difference is 40 μm (94–54 = 40). The tablets made from this mix at 44.0 kN have an averaged tensile strength of 4.2 MPa. This represents the tensile strength of a binary mix containing 15.1% of niflumic acid according to Fig. 2. This is clearly less than the true 50% v/v content of the mix. To go back to the tensile strength of a mix, one has to determine what is its apparent niflumic acid content in Fig. 3 and report this value in Fig. 2 or the corresponding equation.

Figure 3 shows how the organization of a binary mix influences its compactibility. As already determined by electron microscopy, niflumic acid, and ethyl cellulose are two interacting materials. When the blended materials have very different mean particle sizes, the smaller particles will adhere to the coarser ones. Thus, the compactibility of the binary mixes is closer to the compactibility of the adhering material. This is what is observed in Fig. 3a: keeping the particle size of NA constant, the apparent percentage of niflumic acid increases as the particle size of the EC fraction used increases (the mean difference decreases). Similar results were obtained at a lower compression force (9.3 kN), the influencing factor in the apparent percentage of niflumic acid being the mean particle size difference.

The curves in Fig. 3a have identical slopes but different intercepts. It is well known that different sieved fractions of

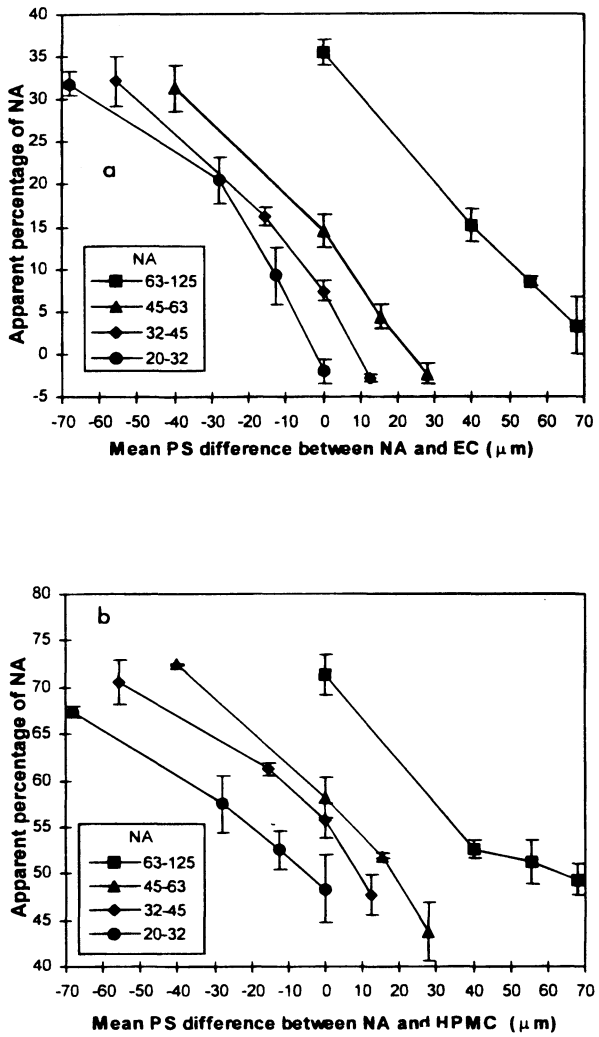

Fig. 3. Apparent percentage of niflumic acid in 50/50 v/v binary mixes of niflumic acid and ethyl cellulose (a) or hydroxypropyl methylcellulose (b) compacted at 44.0 kN as a function of the difference between their mean particle sizes (mean PS). When error bars are not visible, they are included within the size of the symbols.

the same material will give tablets of different tensile strengths. The effect of particle size on the tablet strength is strongly dependent upon the properties of the substance. For acetylsalicylic acid, sodium citrate, and lactose, it was observed that the tablet strength decreased with an increase in particle size, while for sodium chloride and Sta-Rx, the converse applied (13). For Emcompress and saccharose, two materials undergoing extensive particle fragmentation during compaction, the tablet tensile strength was almost independent of variations in particle size. In fact, when a coarse and a fine fraction of α-lactose monohydrate were blended, there was no perfect linear relationship between the composition of the binary mix and the crushing strength of the tablet (14). This suggests differences in fragmentation potential of the particles in the various powder systems. Therefore, it is not surprising that the slopes of the curves are identical but not their intercepts.

When two fractions blended have similar particle sizes, the particles do not interact. Therefore, one could expect the apparent percentage of niflumic acid to be around 50% and

similar for all fractions. This was not observed. Remember that the calibration curves (Fig. 2) were obtained with binary mixes of raw materials. As indicated in Table I, the raw powders of the pure materials did not have similar particle sizes. Given that ethyl cellulose has a larger mean particle size than niflumic acid, some of the crystals of niflumic acid adhered to the particles of ethyl cellulose. Therefore, the mix had an "apparent" content of niflumic acid higher than 50% v/v. This is why all the apparent percentages of niflumic acid obtained from fractions of similar particle size are lower than 50% in Fig. 3. The apparent percentages are not similar as the tensile strength of the mix will depend on the compactibility of the non-interacting sieved fractions. As the particle size decreases, the compactibility increases. For example, looking back at Fig. 3a, when the mean particle size fraction is nil and the particle size fraction of NA decreases, the apparent percentage decreases. Niflumic acid is a poorly compactible material, whatever its particle size, whereas decreasing the particle size of ethyl cellulose greatly enhances its compactibility. Consequently, the apparent percentage of niflumic acid decreases with the particle size of ethyl cellulose.

Blends of Niflumic Acid with Hydroxypropyl Methylcellulose

The results obtained with the NA/HPMC binary mixes at 44.0 kN are presented in Fig. 3b. They confirm that the tensile strength of the binary mix strongly depends on its organization. Again, when a small particle size sieved fraction of niflumic acid is blended with a large particle size sieved fraction of HPMC, the crystals of NA adhere to the fibers of HPMC to form an entity with worse compactibility than when the small fibers of HPMC adhere to the surface of large crystals of NA. As in the case of NA/EC mixtures, all the curves have similar slopes but different intercepts.

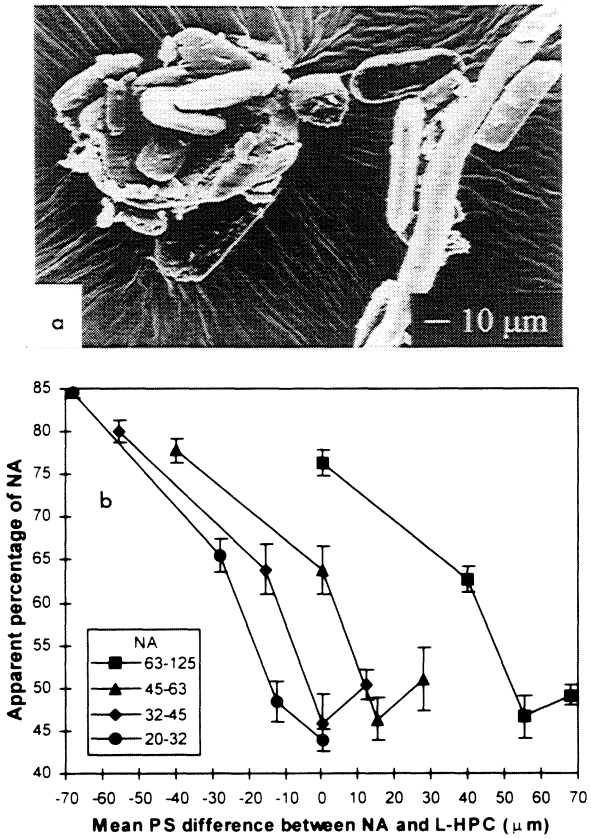

Fig. 4. SEM pictures of the 20–32 μm fraction of niflumic acid blended with the 63–125 μm fractions of L-HPC (a). Apparent percentage of niflumic acid in 50/50 v/v binary mixes of niflumic acid and L-HPC compacted at 44.0 kN (b) as a function of the difference between their mean particle sizes (mean PS). When error bars are not visible, they are included within the size of the symbols.

Blends of Niflumic Acid with a Low Hydroxypropyl Cellulose

Results obtained with this series are quite similar to those of the other series, except that the mixes containing the fractions [63–125 μm] and [45–63 μm] seem to have the same compactibility at both low and high compression forces. Table II indicates the surface energies of the pure materials as well as the $|^{B/A}\lambda - {}^{A/B}\lambda|$ parameter value for each series. The larger the value of $|^{B/A}\lambda - {}^{A/B}\lambda|$, the more the materials interact. Previously, we showed it was possible to relate this parameter and the particle size of the fractions with the organization of binary mixes (2). The NA/L-HPC series is less interacting than the NA/EC and NA/HPMC series. However, when the two fractions have very different particle sizes, the interaction between the two materials is clear (Fig. 4a). Therefore, a larger difference in size between the fractions blended may be necessary to see an effect on the compactibility (Fig. 4b).

For all the series studied up to now, the organization of the mix influences its compactibility. When there is an interaction between two materials, the mix has the compactibility of the adhering material (smallest particle size). As mentioned by Blattner *et al.* (15), as soon as the component with the lower (or higher) mechanical stability percolates through the powder system, tablet hardness is controlled entirely by this component. The percolation threshold is a function of the geometrical arrangement of the particles in the compressed powder system. It is comparable to a phase inversion in an emulsion. This geometrical arrangement is a function of the relative difference between the two spreading coefficients of the materials and of their relative particle size (2).

Blends of Ethyl Cellulose with Hydroxypropyl Methylcellulose

The $|^{B/A}\lambda - {}^{A/B}\lambda|$ parameter is very small for the HPMC/EC series. This means that the two materials do not interact. This is clearly shown by electron microscopy (Fig. 5a). After compression, the binary mixes give tablets of similar tensile strength, i.e., of similar apparent percentage of ethyl cellulose (Fig. 5b). Overall, except for the mixes prepared with the [63–125 μm] fraction of ethyl cellulose, the particle size of the fraction used does not modify the tensile strength of the tablets. This may result from a partial fragmentation of the large and unprotected particles of ethyl cellulose as fragmentation potential is greater for a larger size fraction than for a smaller fraction (16). Since ethyl cellulose consolidates mostly by fragmentation and HPMC consolidates by plastic deformation, when the [63–125 μm] EC/[63–125 μm] HPMC mix is compacted, the relatively small newly formed EC particles may make a partial percolating network, thus artificially increasing the apparent percentage of ethyl cellulose.

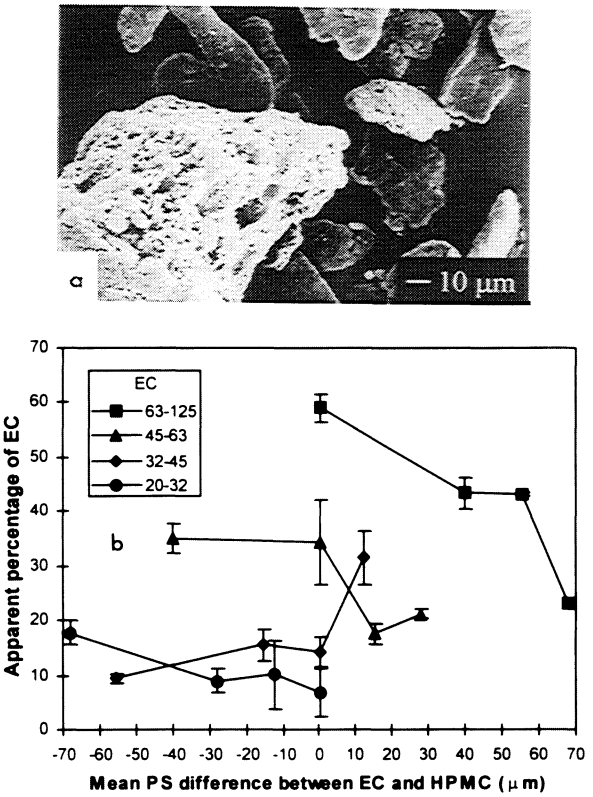

Fig. 5. SEM pictures of the 20–32 μm fraction of HPMC blended with the 63–125 μm fraction of ethyl cellulose (a) and apparent percentage of ethyl cellulose in 50/50 v/v binary mixes of ethyl cellulose and hydroxypropyl methylcellulose compacted at 44.0 kN as a function of the difference between their mean particle sizes (b). When error bars are not visible, they are included within the size of the symbols.

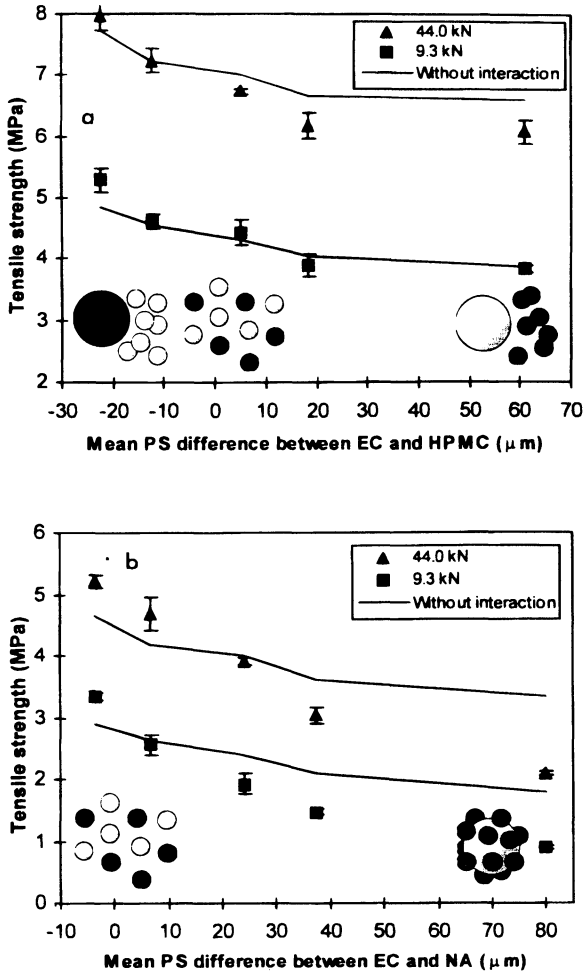

Fig. 6. Experimental tensile strength of HPMC/freeze-milled EC (a) and NA/freeze-milled EC (b) tablets obtained at two compression forces (9.3 and 44.0 kN) compared to the expected value without interaction (in continued line). When error bars are not visible, they are included within the size of the symbols.

Blends of Niflumic Acid with Freeze-Milled Ethyl Cellulose Instead of Sieved Ethyl Cellulose

The results show that when the surface energies of the materials blended allow interactions, it is possible to artificially increase the compactibility of a mix without changing its composition. This could be very interesting, especially when the dosage form contains a relatively high content of a poorly compactible active ingredient. However, from an industrial point of view, sieving is not so straightforward as milling. Therefore, it is of interest to mill a good compactible excipient and blend it with a highly compactible active ingredient to improve the overall compactibility. Several freeze-milled fractions of EC were prepared (particle size: 47.4, 34.0, 16.5, and 6.5 μm) and blended with the HPMC or NA raw materials. The tablet strengths of the tablets obtained at two compression forces are presented in Fig. 6. The continued lines represent the expected tensile strength of the mix when no interaction occurs between the materials. This value was calculated from the tensile strength of each pure fraction and corrected for the proportions used to prepare the mixes (w/w). For the HPMC/EC non-interacting system (Fig. 6a), the experimental tensile strengths were very close to the calculated curves. When the particle size of EC is reduced in the NA/EC interactive system (Fig. 6b), the original organization where the small crystals of NA adhere to the large particles of EC is modified up to the stage where the two materials have similar particle size ranges. Thus, the tensile strengths of the tablets at 9.3 kN and 44.0 are increased 3.7 and 2.5 fold; respectively.

CONCLUSIONS

In a previous work (2), we demonstrated it was possible to control the organization of binary mixes by modifying the particle sizes of the fractions blended if they had the appropriate surface energies. In the present work, the major effect of this organization on the compactibility of the mix has been shown. In the case of interacting materials, the compactibility of a binary mix will depend mostly on the compactibility of the percolating material whereas, when the two materials are not interacting, the mix will have an intermediate compactibility resulting from the influence of both materials. This is a completely new approach that can advantageously implement the traditional method involving the different consolidation mechanism (plastic or brittle) of the materials.

Several industrial applications can be made over these findings. In the development phase, it is possible to modify the formulation of interacting systems to increase the drug content

without losing the compactibility of the mix. In the production phase, it is possible to increase the compactibility of a poorly compactible active ingredient by sieving or preferably by milling an excipient with good compression qualities without changing the composition of the mix.

ACKNOWLEDGMENTS

The authors would like to thank Mrs. C. Michel for her technical assistance in using the scanning electron microscope.

REFERENCES

1. H. Leuenberger. The compressibility and compactibility of powder systems. *Int. J. Pharm.* **12**:41–55 (1982).
2. J. Barra, F. Lescure, F. Falson-Rieg, and E. Doelker. Can the organisation of a binary mix be predicted from the surface energy, cohesion parameter and particle size of its components? *Pharm. Res.* **15**:1727–1736 (1998).
3. S. M. Upadrashta, P. R. Katikaneni, G. A. Hileman, S. H. Neau, and C. E. Rowlings. Compressibility and compactibility properties of ethylcellulose. *Int. J. Pharm.* **112**:173–179 (1994).
4. J. T. Fell and J. M. Newton. The prediction of the tensile strength of tablets. *J. Pharm. Pharmacol.* **22**:247–248 (1970).
5. H. Leuenberger and W. Jetzer. The compactibility of powder systems—A novel approach. *Powder Technol.* **37**:209–218 (1984).
6. L. E. Holman and H. Leuenberger. The effect of varying the composition of binary powder mixtures and compacts on their properties. A percolation phenomenon. *Powder Technol.* **60**:249–258 (1990).
7. S. TakTak-Jama Contribution à l'étude du comportement en compression de poudres et de leurs mélanges: optimisation de leur aptitude à la compression. Ph.D. thesis, University of Lille 1997, pp. 1–231.
8. H. Leuenberger. Compression of binary powder mixtures and solubility parameters of solids. *Int. J. Pharm.* **27**:127–138 (1985).
9. G. D. Cook and M. P. Summers. The tensile strength of aspirin-Emcompress tablets. *J. Pharm. Pharmacol.* **37**:29P (1985).
10. J. M. Newton, D. T. Cook, and C. E. Hollebon. The strength of tablets of mixed components. *J. Pharm. Pharmacol.* **29**:247–249 (1977).
11. S. Majuru and D. E. Wurster. The effect of composition on the tabletting indices of binary powder mixtures. *Pharm. Dev. Technol.*, **2**:313–321 (1998).
12. K. A. Riepma, C. F. Lerk, A. H. De Boer, G. K. Bolhuis, and K. D. Kussendrager. Consolidation and compaction of powder mixtures: I. Binary mixtures of same particle size fractions of different types of crystalline lactose. *Int. J. Pharm.* **66**:47–52 (1990).
13. G. Alderborn and C. Nyström. Studies on direct compression of tablets. IV. The effect of particle size on the mechanical strength of tablets. *Acta Pharm. Suec.* **19**:381–390 (1982).
14. K. A. Riepma, J. Veenstra, A. H. De Boer, C. F. Lerk, and H. Vromans. Consolidation and compaction of powder mixtures: II. Binary mixtures of different particle size fractions of alpha-lactose monohydrate. *Int. J. Pharm.* **76**:9–15 (1991).
15. D. Blattner, M. Kolb, and H. Leuenberger. Percolation theory and compactibility of binary powder systems. *Pharm. Res.* **7**:113–117 (1990).
16. N. A. Armstrong and T. M. Cham. Changes in the particle size and size distribution during compaction of two pharmaceutical powders with dissimilar consolidation mechanisms. *Drug Dev. Ind. Pharm.* **12**:2043–2059 (1986).