DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(12), 1393-1411 (1993)

Indices of Tableting Performance for Acrylic Resin Polymers with Plastic and Brittle Drugs

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Abstract The indices of tableting performance were used to investigate the compaction properties of two methacrylate ester copolymers (Eudragit® RS PM and RL PM) and three methacrylic acid copolymers (Eudragit® S 100, L 100, and L 100-55). These polymers were designed to be incorporated directly into solid dosage forms for controlled-release purposes. The polymers were combined in the dry state with either sodium sulfathiazole (a brittle drug) or theophylline (a plastic drug) at concentrations ranging from 0 to 100% polymer. All powders were blended for 15 minutes and compacts measuring 1 inch square and weighing 5 g each were made using a die that decompressed triaxially and a Carver® press equipped with a strain gauge. Solid fractions were kept constant at 0.81. Two of the tableting indices, the bonding index (BI) and brittle fracture index (BFI), were studied for all mixtures. The BFI of the sulfonamide (0.49) was nearly three times greater than the BFI for theophylline(0.17) The three methacrylic acid copolymers had high BFI values ranging from 0.99 to 1.60, demonstrating the brittle characteristics of these polymers. The BFI decreased with increasing drug content in all cases. Of the five polymers, the BI was greatest for Eudragit® L 100-55 with both drugs, especially at the 20% drug concentration, followed by Eudragits L 100 and S 100. These three resins were prepared by a spray-drying process. The strongest interactions (positive deviations for the BFI; negative deviations for indentation hardness and BI) of either drug with the polymers were always seen with the spray-dried materials. Low bonding indices were obtained for both of the methacrylate ester copolymers. However, all mixtures of both drug with these milled polymers (RL PM and RS PM) formed successful tablets.

Introduction

The two most important tableting indices used in quantifying compaction properties of powdered solids are the bonding index (BI) and the brittle fracture index (BFI). There are many physical properties of compacts (e.g., tensile strength, shear strength, elastic properties, and hardness) that are of interest to the formulation scientist involved in the production of solid dosage forms. However, most of the examples cited involving physical testing of compacts result in absolute values that could be significantly affected by the manner of testing, including type of apparatus, method used, tablet orientation, and operator influence. A reduction of these values to a dimensionless form before making comparisons may offer more insight into the fundamental characteristics of different materials. Recent publications suggest the increasing acceptance of the tableting indices as a viable testing method in the pharmaceutical field. In 1984, Hiestand and Smith described the theory behind the indices and reported on the compaction of several drugs and excipients in their pure states, citing several examples of materials known to pose tableting problems indicated as such by their index values.[1] A significant advantage of this technology is that small quantities (grams as compared to kilograms) are required to characterize a material or a solid blend. This is particularly important in the developmental stage of a new compound when quantities are limited and the material is expensive. Since the physical-mechanical properties of a blend of materials is not additive, the application of the tableting indices in preformulation could optimize excipient selection in order to increase the bonding index and decrease the brittleness of a resulting compact. In 1988, the bonding index and brittle fracture index were shown to be useful in describing a binary powder combination of calcium sulfate and magnesium stearate.[2] In another study of binary mixtures using the tableting indices, Williams and McGinity[3] reported on the compaction properties of microcrystalline cellulose and sodium sulfathiazole with varying concentrations of talc or magnesium stearate. More recently, Schulze and coworkers[4] have described the tensile strengths of compacts composed of acrylic resin polymers together with theophylline and sodium sulfathiazole.

Acrylic resin polymers have been in use in the pharmaceutical industry for over a quarter of a century as pharmaceutical coatings. More recently, these materials have been investigated in direct compression formulations as controlled-release matrix-formers.[5-10] With the increasing use of direct compression excipients in tableting blends, the need to fully quantify their performance is mandated. It is the objective of this report to characterize the brittle and bonding characteristics of five of the directly

compressible Eudragit® acrylic resin copolymers together with either a model plastic drug (theophylline) or a model brittle compound (sodium sulfathiazole) using the brittle fracture and bonding indices. To this end, the dynamic indentation hardness necessary for the calculation of the bonding index, is also reported.

Experimental Section

The following acrylic resin polymers used in these investigations were obtained from Röhm Pharma GmbH, Darmstadt, Germany: Eudragit® RS PM, RL PM, S 100, L 100, and L 100-55. Sodium sulfathiazole and theophylline anhydrous were obtained from Sigma Chemical Corporation, St. Louis, MO.

All powders were sized through a number 30 mesh screen prior to use. Powders for binary mixtures were blended for 15 minutes in a twin shell V-blender. Powder samples weighing 5 g were used for each compact. All compacts were made using a specially modified Carver® laboratory press, as described earlier.[2,3] Square, flat-faced punches measuring 1 inch on each side were employed for indentation hardness testing and tensile testing. Such compacts provide a greater volume of material around the point of contact of the spherical indentor used for indentation hardness testing and yielded more reliable tensile test results. The square die used to make the compacts was split along a line through one diagonal and was capable of triaxial decompression as the compression pressure was released.

To optimize the comparison of test results for different materials, a constant solid fraction (rather than constant compression force) was used to provide more similar states of consolidation. The solid fraction (relative density) was obtained first by measuring the thickness of compacts after ejection from the die in order to calculate its volume. To calculate the relative density or solid fraction, the apparent density (calculated from the weight and volume of the compact) was divided by the true density of the powder(s) from which the compact was made. The true density of a powder was obtained with a helium pycnometer (Micromertics Model 1302, Norcross, GA). Pure materials and binary blends with concentrations at 20% increments were prepared for testing. Dynamic indentation testing was performed with a pendulum impact apparatus to determine the dynamic indentation hardness of compacts. The BI, BFI and dynamic indentation hardness values were determined from the mean of four measurements. The pendulum impact apparatus was a modification of the equipment originally described by Hiestand and Smith,[1] and was previously described by Williams and McGinity.[2,3]

Results and Discussion

The brittle fracture index is obtained by comparing the tensile strengths of tablets with and without a small, axially oriented hole at the center of the compact. The equation for the brittle fracture index, normalized to give values between zero and one, is as follows:

$$BFI = \frac{1}{2} \cdot \left(\frac{\sigma_T}{\sigma_{To}} - 1 \right) \quad (1)$$

where σ_T is the tensile strength of the compact and σ_{To} is the tensile strength of the compact with the stress concentrator. The purpose of the stress concentrator is to weaken the compact to a degree proportional to its brittle character. The basis for the brittle fracture index lies in the Griffith crack theory. According to this theory, tensile fracture might be expected to occur at exactly one-third of the tensile stress required to produce tensile fracture when no hole is present in a perfectly brittle material.[1] Such a fracture by crack propagation from a flaw that concentrates stress is called brittle fracture. Most materials possess at least some ability to deform plastically and would fracture at some intermediate value, the magnitude depending on their ability to relieve localized stresses.

The brittle fracture index calculation is based on the differences in tensile strength for compacts with and without stress concentrators. Values for the brittle fracture indices for compacts of sodium sulfathiazole and the Eudragit® copolymers are shown in Figure 1. Several of the polymers are of an exceedingly brittle nature, as evidenced by their very high brittle fracture indices. The three spray-dried Eudragit® methacrylic acid copolymers (L 100, L 100-55, and S 100) have values of 1.603, 1.193, and 0.985, respectively. Theoretically, any material with a brittle fracture index of 1.0 is a material that undergoes very little plastic deformation[11] and, while values greater than 1.0 are possible, they are uncommon.[11,12] Hiestand and Smith[1] obtained brittle fracture indices ranging from 0.04 for the highly compressible excipient, Avicel® PH 102, to values of 0.83[1] and 0.98[11] for the brittle drugs, erythromycin dihydrate and methenamine, respectively.

Sodium sulfathiazole, with a brittle fracture index of 0.488, was intermediate in brittleness when compared to the polymers analyzed in this study. The presence of even relatively small percentages of Eudragit® RL PM or RS PM copolymers in these compacts markedly reduced the value of the brittle fracture index. Eudragit® RL PM and RS PM each modulated the brittle nature of the sodium sulfathiazole in their respective

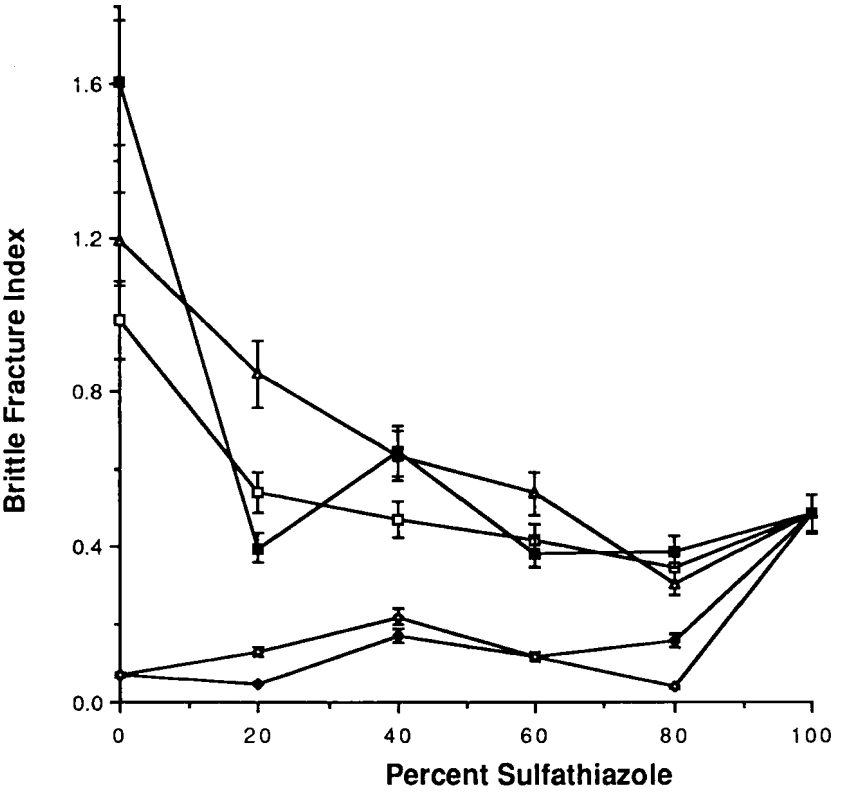

Figure 1: The brittle fracture index (mean ± SD) of sodium sulfathiazole/Eudragit® compacts. Key: (□), L 100-55; (■), L 100; (Δ), S 100; (◆), RL PM; (◇), RS PM.

compacts up to a drug content of 80%. Even at this level, the RS PM polymer decreased the brittle fracture index of sodium sulfathiazole from a value of 0.488 to one of 0.040 (over a tenfold reduction); The RL PM compacts containing 20% polymer exhibited a brittle fracture index of 0.161, which was still greater than a threefold decrease in brittleness. In some of the dynamic indentation testing procedures, compacts of sodium sulfathiazole laminated, resulting in an inability to record values for the test. Lamination is a reflection of insufficient bonding within the tablet, which allows crack propagation, begun by an external stress, to proceed throughout the tablet. If sufficient plastic deformation occurs at the bonded areas such that stresses developed by elastic recovery do not exceed bond strength, the bonds will survive. However, if the disruption is sufficient (or if inadequate plastic flow has occurred), the integrity of the tablet will be destroyed.

The addition of sodium sulfathiazole markedly reduced the brittleness of the methacrylic acid copolymers, resulting in brittle fracture index values lower than expected. Eudragit® L 100, with the highest index value of about 1.6, was reduced to a quarter of its original value with the addition of only 20% sodium sulfathiazole; Eudragit® L 100-55 and S 100 were decreased in brittleness by an amount proportional to the quantity of sodium sulfathiazole added. Jetzer[13] found that for binary mixtures, the compaction characteristics were principally directed by the behavior of the individual materials and that interactions were to be expected with mixtures of components with dissimilar compaction mechanisms. He suggested that the more readily deformable component predominantly undergoes plastic deformation, whereas the other substance changes little in shape and becomes encapsulated until enough brittle particles are available for that mode of consolidation to become apparent. Binary powder mixture A/B forms (at intermediate volume concentration ratios) an interpenetrating network of particles of component A and B. Thus it is not surprising that for certain binary powder systems, clearly recognizable changes in the compaction behavior occur as soon as one of the components forms a continuous network around the other as the compaction stress is transmitted by particle - particle contacts. This mechanism could explain the marked improvement in compaction behavior upon the addition of small amounts (20%) of either RL PM or RS PM to the brittle drug sodium sulfathiazole, as seen in Figure 1.

When compared to Eudragit® L 100, L 100-55, and S 100, the methacrylate ester copolymers RL PM and RS PM have much lower (and nearly identical) brittle fracture indices of 0.070 and 0.071, respectively. These low values can be attributed to the ease with which plastic flow and consolidation occur. Theophylline, with a low brittle fracture index value of 0.170, is also a relatively plastic material and displayed good compaction characteristics. The brittle fracture index values for compacts of theophylline and the Eudragit® copolymers are shown in Figure 2. Previously reported positive tensile strength deviations resulted in decreased values in the brittle fracture index for the mixtures of theophylline and the brittle copolymers[4]. The compacts of Eudragit® RS PM and, to a lesser extent, RL PM exhibited an approximate linear relationship for blends between pure polymer and pure theophylline. Linear regression analysis for the theophylline:RS PM data produced a correlation coefficient of 0.9.

These results reveal some of the complexities that can occur when mixtures of powders are subjected to compressional forces. Roberts and Rowe[14] studied the physical properties of tablets based on a number of variables, including initial particle size of the powders used. Materials that exhibit both brittle and ductile behavior involve an initial decrease in compressibility as particle size decreases. At a transition point, flow

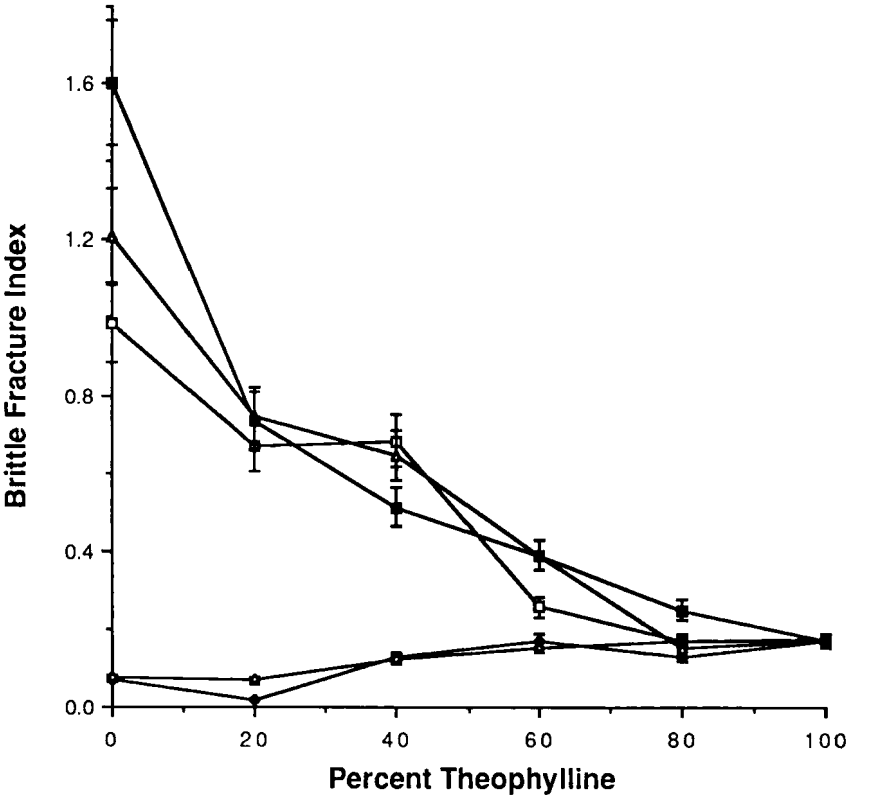

Figure 2: The brittle fracture index (mean ± SD) of Eudragit®/theophylline compacts as a function of composition. Key: (□), L 100-55; (■), L 100; (Δ), S 100; (◆), RL PM; (◇), RS PM.

follows fracture and compressibility becomes independent of any further decreases in particle size. Other research has revealed that decreasing the particle size of a material generally results in an increased crushing strength for tablets, although this was highly dependent upon the materials tested and the method of consolidation.[15] The number of points of contact (and hence potential bond strength) depends to some extent on the particle size spectrum, and particle size differences will modify density and tablet thickness. Particle size analyses for the drugs and polymers used in this study indicated roughly equivalent sizes and distributions, with the largest fraction of each falling within the 50 to 200μm range. Although particle sizes were not varied with the materials studied in the present work, the complexity of compression is such that the potential influence particle size may exert upon the tableting process should be acknowledged.

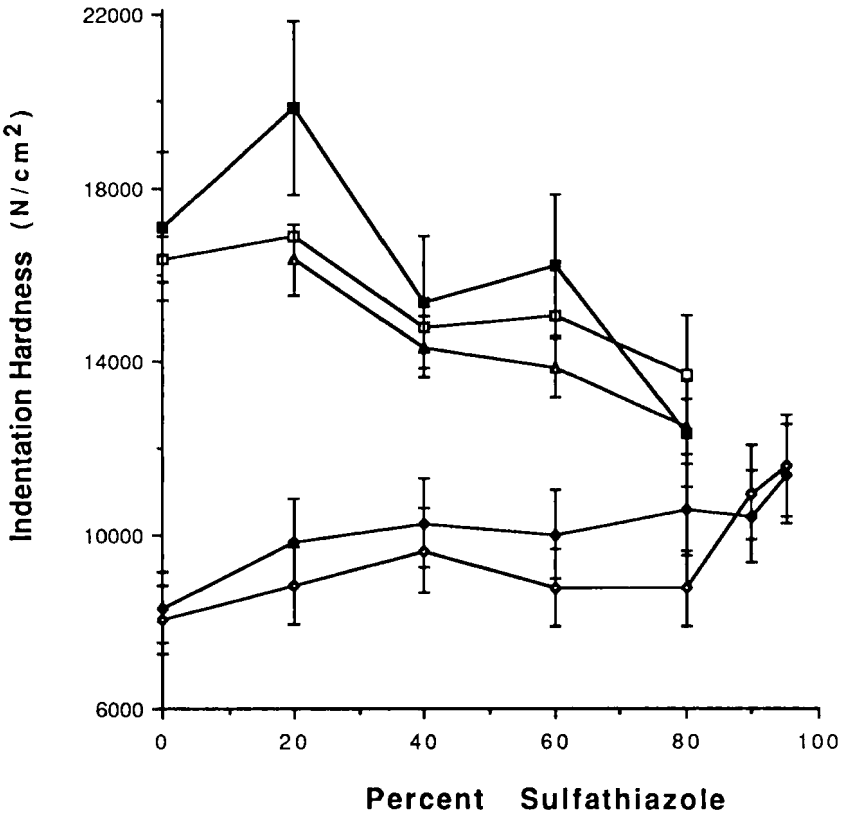

Figure 3: Dynamic indentation hardness (mean ± SD) for compacts of Eudragit® copolymers and sodium sulfathiazole. Key: (□), L 100-55; (■), L 100; (△), S 100; (◆), RL PM; (◇), RS PM.

The indentation hardness P was obtained by an impact method described by Tabor[16] which readily provides both the mean pressure under the indentor (indentation hardness) and the magnitude of the elasticity parameter, E. Using this dynamic indentation apparatus, the value for P was calculated from the following equation:

$$P = \frac{4mgrh_r}{\pi a^4} \cdot \left(\frac{h_i}{h_r} - \frac{3}{8}\right) \qquad (2)$$

where m is the mass of the indentor, a is the radius of the dent, g is the gravitational constant, r is the radius of the indentor, h_i is the initial height of the indentor, and h_r is the rebound height. Hiestand, Bane, and Strzelinski[17] have described in detail the impact-rebound method for estimating the hardness of compacts.

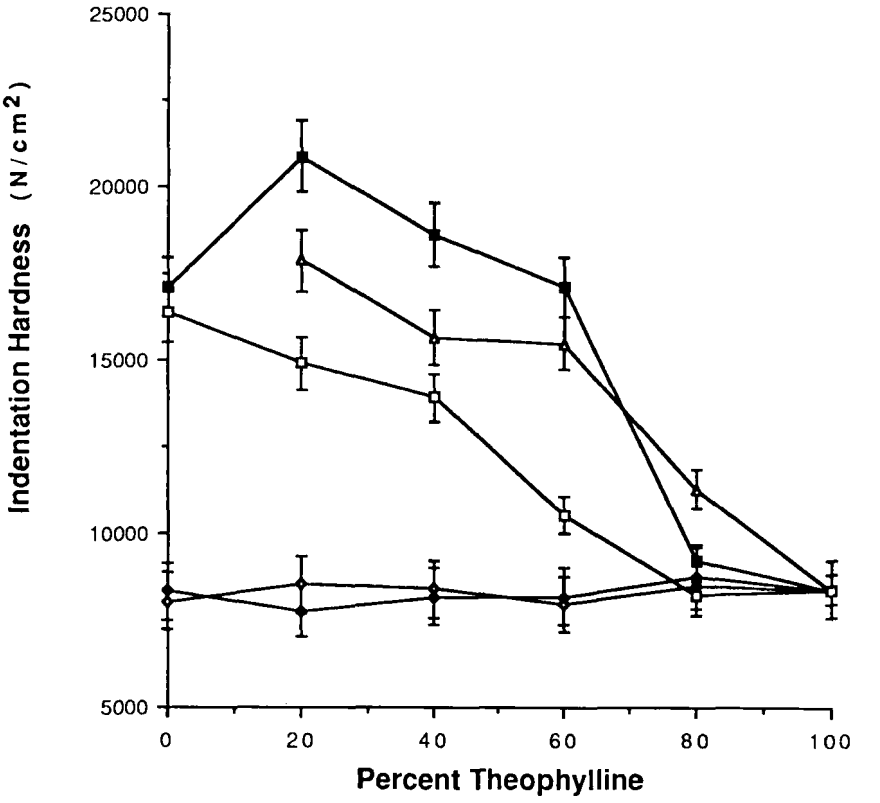

Figure 4: Dynamic indentation hardness (mean ± SD) of theophylline and Eudragit® compacts. Key: (□), L 100-55; (■), L 100; (△), S 100; (◆), RL PM; (◇), RS PM.

The indentation hardness values (expressed as N/cm^2) for each of the Eudragit® polymers were plotted against the percent of sodium sulfathiazole in the compacts as found in Figure 3. The compacts that consisted of pure sodium sulfathiazole and Eudragit® S 100 demonstrated low bonding properties as indicated by the low bonding indices (see Fig. 5). This, together with their brittle nature, caused the compacts to laminate under the stress of indentation. Compacts did hold together for tensile testing, but upon impact from the steel sphere during indentation testing, the compacts laminated, rendering them unusable. Subsequently, the hardness of the tablets could not be measured, resulting in missing data points for the Eudragit® S 100 and sodium sulfathiazole compacts in Figure 3. The missing data involve the concentration range of "0% < C < 20%", of sulfathiazole which should roughly correspond to a "sulfathiazole

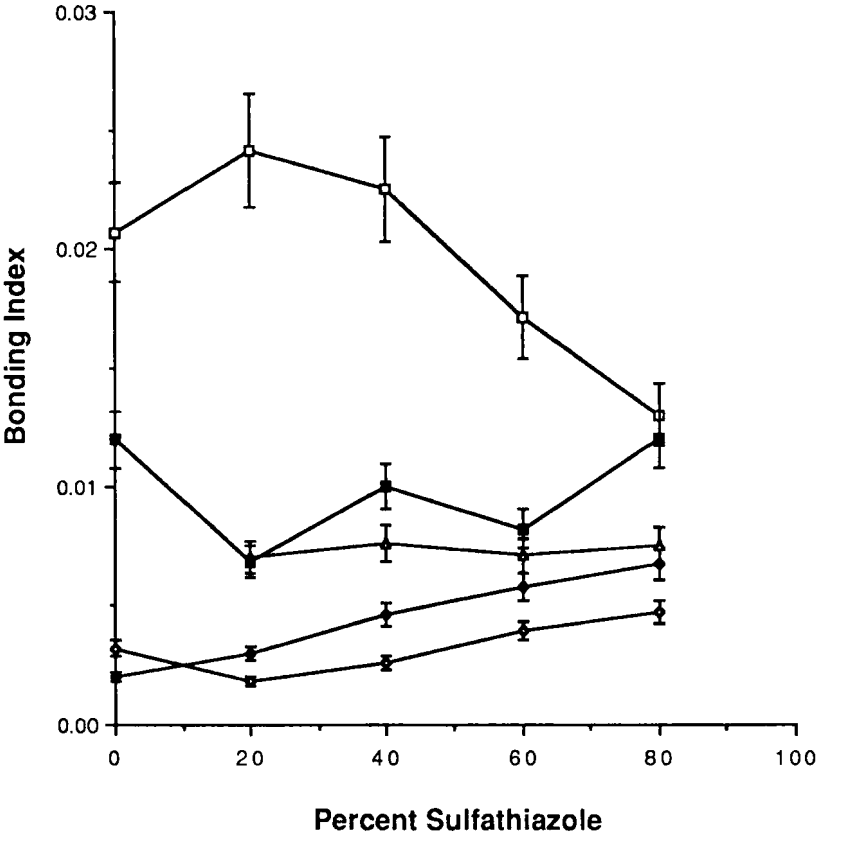

Figure 5: The bonding index (mean ± SD) for sodium sulfathiazole and Eudragit® copolymer compacts. Key: (□), L 100-55; (■), L 100; (Δ), S 100; (◆), RL PM; (◇), RS PM.

in Eudragit S 100 mixture" and range "80% < C < 100%" sulfathiazole, which should roughly correspond to an "Eudragit S 100 in sulfathiazole powder mixture". Assuming spherical particles of equal size are randomly mixed, one particle touches twelve others. In a 50:50 mix of "A" and "B", an "A" particle will touch (and bond under pressure) six other "A" particles and six "B" particles on average. The same holds for each "B" particle in the blend. Thus, both A-A and B-B networks are formed in addition to the A-B bonds. At the 20% "A" level in an A-B mixture, the number of A-A bonds drops to 2.4 per particle, but a coherent network could still result. Below 20%, a bicoherent network becomes more unlikely as B-B bonds make up the vast majority of those formed with smaller and smaller pockets of "A" particles and A-A bonds. In the case of the

intermediate concentrations, the bicoherent network of sulfathiazole and Eudragit S 100 powder particles provided tablets which were adequate for the indentation hardness test. Combinations of polymer and drug yielded reproducible results with most of the coefficients of variation in the 5 to 10% range. The combinations of the brittle methacrylic acid copolymers (Eudragit® L 100 and L 100-55) together with the brittle drug sodium sulfathiazole constituted exceptions in this category. The improved bonding for the sodium sulfathiazole:L 100 compacts and the compacts containing L100-55 resulted in harder compacts compared with the drug:S 100 compacts. As can be seen in Figure 5, the bonding indices for the L 100-55/drug combinations were significantly higher than those containing S 100 in every case; the bonding indices for the L 100 containing compacts were higher for three of the four blends examined. These combinations yielded the hardest tablets of those tested. While hardness is a desirable property for mechanical strength, these hard compacts were also very brittle, as evidenced by their higher brittle fracture indices, making the compacts weaker against fracture. It should be noted that there was no correlation between compression force and indentation hardness for these blends.

For the spray-dried methacrylic acid copolymers, the addition of sodium sulfathiazole generally decreased the dynamic indentation hardness, although some "sawtooth" deviations were seen with compacts containing Eudragit® L 100. The initial rise in hardness may be attributed to the rise in surface area due to fragmentation of one of the components, followed by a decrease resulting from interparticulate bonding as particles are pressed closer together. The secondary increase may be due to the fracture of the second component as its concentration increases. Armstrong and Griffiths[18] noted such patterns in their work relating surface areas and compression for granules made from the brittle drugs phenacetin and paracetamol (acetaminophen). Compositional changes could have similar effects.

Dynamic indentation hardness values for the pure polymers varied according to the class of polymer to which they belonged. The methacrylate ester copolymers (Eudragit® RL PM and RS PM) were the softest of the two groups of Eudragit® copolymers, with hardness values of about half those of the methacrylic acid copolymers. This was not unexpected since harder materials are generally much more brittle than their softer counterparts. For members within each of these two classes, values for the individual polymers were within 5% of each other. The similarity in dynamic indentation hardness can be viewed as a reflection of the chemical similarities of the polymers within a given group.

The indentation hardness of resin compacts containing increasing amounts of theophylline in the compacts is shown in Figure 4. Of particular interest is the

observation that mixtures of theophylline and Eudragit® L 100 compacts yielded indentation hardness values that were much higher than those for either of the two materials alone where the theophylline concentration C was 20% ≥ C ≥ 80%, i.e. in the range where both powder particles form a bicoherent interpenetrating network. At a concentration of 80% and higher, the indentation hardness was roughly identical with the hardness of pure theophylline compacts. Peaks for compacts of Eudragit® copolymers with theophylline were more pronounced than those of the sodium sulfathiazole and copolymer blends. A smooth peak (in contrast with the sawtooth effect seen for sulfathiazole mixtures) was observed with theophylline and Eudragit® L 100 compacts. This indicates an absence of fragmentation for the plastic theophylline component. These increased hardness values were a logical extension of the higher tensile strengths seen previously,[4] since strength and hardness generally are common properties of a material. According to Newton and coworkers,[19] the presence of a higher strength (and hence hardness) than predicted implies that the bond between the differing materials is in fact stronger than that between the individual materials, themselves. Increased strength, in addition to more pronounced brittle characteristics, has previously been reported with other drug and polymer combinations. Jetzer and coworkers[20] studied the compression properties of binary mixtures and found deviations for P_{max} (a deformation resistance parameter) as well as Brinell hardness values, when these parameters were plotted against the composition ratios of the different materials. The authors attributed this behavior to the introduction of crystal defects into the highly plastic, isotropic, ionic crystals of KBr and KCl. As occurred with tensile strength, the types of interactions which impact hardness values were closely related to the binding properties of the components making up the compact. Positive deviations were more probable with brittle and plastic blends. Furthermore, in the case of positive hardness deviations, it was possible that bonds were formed preferentially between unlike components (drug-polymer). Those bonds occurring between the like materials (drug-drug or polymer-polymer) were less likely to occur or were weaker in magnitude.

Theophylline, with a dynamic indentation hardness of approximately 8400 N/cm2, could not be directly compared to sodium sulfathiazole since compacts of the latter drug laminated during testing, as previously mentioned. However, by extrapolating the hardness values for sodium sulfathiazole and polymer compacts at the higher percentages of drug, a rough estimate of about 12,000 N/cm^2 was obtained. Sodium sulfathiazole was found to be much harder than theophylline, which was expected since sodium sulfathiazole is also a more brittle compound.

The bonding index (BI) was calculated from the tensile strength (σ_T) of a compact divided by its indentation hardness (P):

$$BI = \frac{\sigma_T}{P} \qquad (3)$$

Since physical measurements of strength will reflect the influence of both entities, the calculation of the bonding index has been developed around the carefully selected procedures of tensile testing of square compacts and compact strength under a compressive load. Since it combines the effects of two competing mechanical responses—deformation (indentation hardness) and fracture (tensile strength)—the bonding index reflects the fraction of the strength that survives decompression.

The bonding index was used to estimate the survival of true areas of contact (bonded areas) that were established at maximum compressive stress. Bonding must occur at true contact areas that exist between particles. Bond success would correlate with the combined effect of (1) the areas of true contact that survive the decompression process and (2) the processes during surface separation that influence the manifested strength of the area of true contact. The bonding index utilizes physical measurements of strength, which reflect the influence of both. The tensile strength is an indication of the strength of the compact after decompression; indentation hardness is a measure of the strength under a compressive load, obtained by bouncing a steel sphere off the surface of the compact. The mean pressure (indentation hardness as measured in units of pressure) under the spherical indentor is an indicator of the shear strength under a compressive load. Sufficient force should be used to produce some additional consolidation under the indentor for even the hardest compacts tested.

The determination of the tensile strength was important since the experimental value depends on the procedure used. With viscoelastic materials (as virtually all organic pharmaceutical materials are) the value would also depend on the rate of strain during the test procedure. For this test, the procedure chosen was the transverse compression of square compacts, which was proven to succeed more often than the diametral compression of round tablets.[21] The advantage of this test was that it applied the maximum stress to the very center of the compact, thus measuring the maximum tensile strength at its center. This value was used in a ratio with the indentation hardness, which was also measured at the center of the tablet. In order to minimize the effects of strain rate on viscoelastic materials, a time constant was applied to the tensile test by measuring stress application from initial contact until fracture occurred. After fracture, both the time of the fracture and the time when the applied stress was equal to

1/e times the fracture stress were noted. The time difference between these two periods was arbitrarily chosen to be 10 seconds.

The bonding indices for compacts of sodium sulfathiazole and Eudragit® compacts are illustrated in Figure 5. No values for Eudragit® S 100 or 100% sodium sulfathiazole are included since, as discussed previously, the indentation testing necessary for the calculation of the bonding index could not be performed. An extrapolation of values for compacts whose content approaches that of the respective pure materials allows an estimation of their magnitude. Using this method, it was found that the bonding index for sodium sulfathiazole and Eudragit® S 100 were both about 0.007. This is a low value for the bonding index. It has been postulated that for every powder system the pore network may be considered as one of the components.[22] For brittle substances such as sodium sulfathiazole and some of the Eudragit® copolymers, that consolidate mainly through fragmentation, the pores making up a network may serve to function as stress concentrators, leading to crack propagation and low bond strength. The dependence of the interparticle force of surface separation has been cited as one of the two major factors in determining the bond strength within compacts.[23] In conjunction with the high brittle fracture indices for these two materials (0.49 for sodium sulfathiazole and 1.209 for Eudragit® S 100), capping or lamination under the stress of indentation testing was a logical consequence. In the cases where compacts could not be formed at the selected solid fractions, high BFI values and a tendency towards low bonding were noted, e.g., sodium sulfathiazole and Eudragit® S 100. Blends of these two materials, while still forming compacts, would suggest possible tableting difficulties in the less forgiving environment of a high-speed tablet press. By comparison, the highly compressible and strongly bonding material, Avicel® PH 102, yields a bonding index of 0.04. It has been suggested that the brittle fracture index for materials with low bonding indices should be less than 0.2.[24]

The largest values for the bonding index were seen with compacts composed of the Eudragit® L 100-55. Compacts containing 20% and 40% Eudragit® L 100-55 had the highest bonding index values of all the sulfathiazole blends. These blends yielded values that were higher than those of either of the two starting materials alone, indicating that a preferential drug-polymer bonding was occurring. Although both materials are brittle substances, bonds formed in the combined powders upon compression were strong enough to overcome the tendency to fracture. The remaining acrylic resin polymer combinations (Eudragit® RS PM and RL PM with the two drugs) exhibited approximately linear bonding index/composition relationships from pure polymer to pure drug.

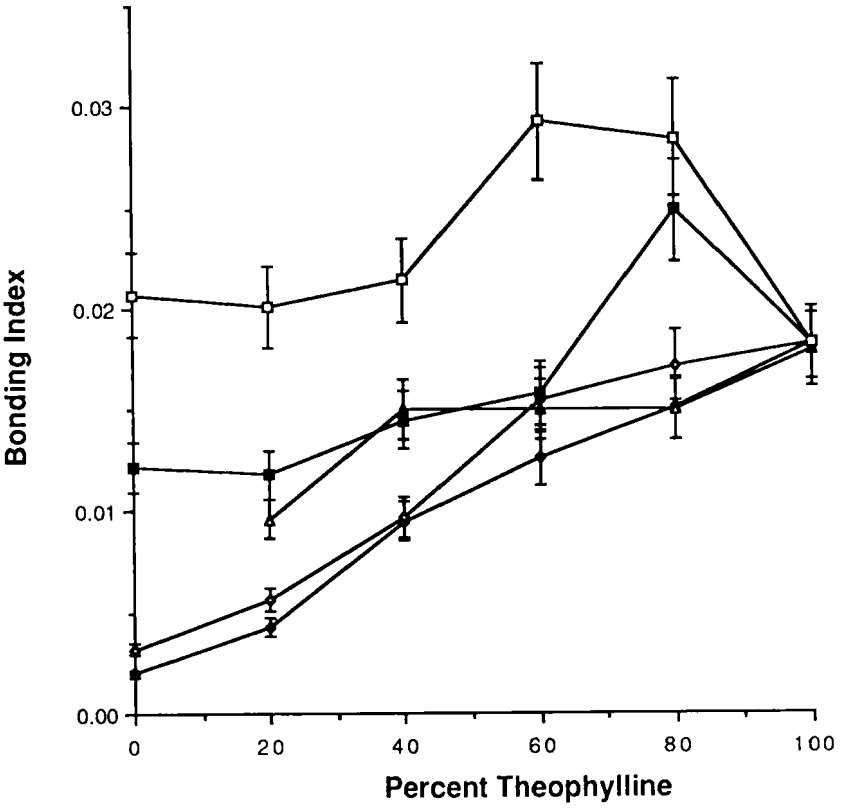

Figure 6: The bonding index (mean ± SD) for theophylline and Eudragit® copolymer compacts. Key: (□), L 100-55; (■), L 100; (Δ), S 100; (◆), RL PM; (◇), RS PM.

The bonding index for theophylline and Eudragit® copolymer resin compacts are shown in Figure 6. The increase in bonding for the L 100 and L 100-55 compacts is probably attributable to the changing mechanisms involved in plastic-brittle blends (theophylline-Eudragit® L 100-55 compacts). Similar patterns were seen by Rohera et al.,[25] who were able to show experimentally that for binary blends of dissimilar materials (such as plastic and brittle substances) the soft component was squeezed out under pressure and encapsulated the brittle component completely. This may place the theophylline and resin in sufficiently intimate contact for the more favorable drug-polymer bonding to occur.

The distinction between the two classes of Eudragit® acrylic resin copolymers was not as clear for the theophylline-Eudragit® blends as it was for the sodium

TABLE 1 - Brittle Fracture Index and Bonding Index of Theophylline and Sodium Sulfathiazole, and Directly Compressible Acrylic Resin Polymers

Material	Brittle Fracture Index	Bonding Index
Theophylline	0.17	0.018
Sodium Sulfathiazole	0.49	*
Eudragit RL PM	0.07	0.002
Eudragit RS PM	0.07	0.003
Eudragit L100-55	0.99	0.02
Eudragit S100	1.20	*
Eudragit L100	1.60	0.012

* Indentation hardness could not be determined for these materials.

sulfathiazole and Eudragit® compacts (see Figure 5). The three methacrylic acid copolymers had the highest bonding indices in virtually every case, and only for 60% and 80% theophylline blends were bonding values for the classes interspersed. Compacts containing the brittle polymers Eudragit® L 100-55 and L 100 had the highest bonding indices in combination with both drugs investigated. This is in agreement with the work of Hiestand and Smith,[1] who found that high bonding index values occurred in materials that were also brittle in nature when similar solid fractions were used. Although the polymers were brittle, they possessed a larger shear strength, as seen from the high hardness values, which was another reflection of the superior bonding in these compacts. Coffin-Beach and Hollenbeck[26] studied the compaction properties of a brittle material (DiTab®) and commented that at lower pressures, particles fractured and rebonded to an equal extent. At higher pressures, however, once the majority of fracture within the powder bed had occurred, more particles began to recombine and bond. This could explain the high bonding index values seen with the more brittle copolymer blends at higher compressional loads.

Eudragit® RL PM and RS PM appear to have the lowest bonding indices in most cases; however this tableting prospect is not so discouraging as might first be

anticipated. The low brittle fracture indices for both of these polymers contributed to successful intact compacts in every case. A large amount of plastic flow was apparently occurring under compression with the Eudragit® RL PM and RS PM. Thus, sufficient bonding within the compacts does occur which limits the disruptive effects of any elastic recovery that may occur after compression, and successful tablets result. It should again be emphasized that these two tableting performance indices (the bonding and brittle fracture indices) should be considered together whenever classifying a material or blend with regard to its ability to form a tablet.

Conclusions

The bonding and brittle fracture indices have been used to study the compaction properties of five acrylic resin polymers and two model drugs alone, and in binary combinations of drug and polymer. Theophylline was demonstrated to be more plastic than the sodium sulfathiazole and the Eudragit® L100 was the most brittle of the five resins studied. The L100-55 and S100 polymers were also shown to be very brittle, whereas the Eudragit® RSPM and RLPM relieved stress by plastic deformation. For the three brittle methacrylic acid copolymers, the addition of the theophylline produced a rapid decrease in the BFI and when 40% or less of these polymers were present with this plastic drug, a BFI of less than 0.4 was reached. This represented a 75% decrease in the BFI for the Eudragit® L100 (1.6). The BFI studies demonstrated that for these acrylic resin polymers, the most brittle was the Eudragit® L100 > L100-55 > S100 > RLPM = RSPM. However, when less than 80% polymer was present in the compacts, insignificant differences were seen in the BFI values for combinations of theophylline with each of the spray-dried polymers.

The sodium sulfathiazole with a BFI of 0.49 was significantly more brittle than the BFI for theophylline (0.17). The sodium sulfathiazole, however, was still able to significantly decrease the brittleness of the methacrylic acid co-polymers in the ratios of drug:polymer that were investigated. The highest bonding index for the acrylic polymers was Eudragit L100-55 > L100 > RSPM > RLPM. Due to either lamination or distortion of the compacts, bonding index values for sodium sulfathiazole and Eudragit® S100 alone were not calculated since indentation hardness values could not be determined. The unsuccessful attempt to obtain a bonding index for sodium sulfathiazole and Eudragit® S100, suggested that these materials should be formulated with plastic excipients or drugs, respectively, in order to form well-bonded compacts. The bonding index data also demonstrated that at higher theophylline levels and low polymer concentrations, well-bonded compacts were formed from all five acrylic polymers.

Presently, the use of tableting indices to optimize the compaction properties of formulations does present some challenges. Only a very limited data base exists with which to compare results in order to determine whether or not observed trends generally hold for other similar compounds or mixtures. Tablet index studies also yield the most accurate results at higher solid fractions (high compression forces). These pressures are generally higher than those employed on rotary tablet presses. Ideally one should choose a solid fraction close to that of the desired final product, if known.

The best candidate for compression is a material or blend that exhibits a high bonding index coupled with a low brittle fracture index. The results of this study suggest that some difficulties may arise with materials or blends with high BI/high BFI or low BI/low BFI combination results. Generally speaking, the lower the BFI value, the better in such circumstances. Thus, the best to worst materials would lie in the following order: high BI/low BFI, low BI/low BFI, high BI/high BFI. As demonstrated in the present studies, the compaction properties of the active ingredient can significantly impact the compaction properties of other ingredients in the formulation.

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