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COMPACTION PROPERTIES OF ACRYLIC RESIN POLYMERS WITH PLASTIC AND BRITTLE DRUGS

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ABSTRACT

Tensile strengths of compacts consisting of acrylic resin polymers in combination with a plastic drug (theophylline) and a brittle drug (sodium sulfathiazole) were investigated. The polymers studied included Eudragit RS PM, RL PM, S 100, L 100, and L 100-55. All compacts were compressed to a solid fraction of 0.81. The solid fraction, rather than compression force, was kept constant in order to account for the differences in packing characteristics and elastic and plastic deformational properties of different materials (1). Tensile strength profiles for the blends of the Eudragit S 100 and RL PM polymers with sodium sulfathiazole included approximately linear relationships between pure drug and pure polymer. The Eudragit L 100-55 exhibited a large peak in the tensile strength of compacts containing 20% sodium sulfathiazole. Significant differences between the physical-mechanical properties of the methacrylate ester and methacrylic acid copolymers were observed where the latter proved to be much stronger at all concentrations. The differences between the two categories of polymers were greater in compacts containing the plastic drug, theophylline. Peaks in tensile strengths were seen for both drugs with all three of the methacrylic acid copolymers, while the methacrylate ester copolymers maintained approximately linear relationships for all ratios of drug and polymer.

INTRODUCTION

Acrylic resin polymers have been used for more than twenty-five years as pharmaceutical coatings, and have been examined in direct compression formulations as controlled release matrices (2-8). Direct compression formulations have many advantages over wet granulations in dosage form design. The development of improved directly compressible excipients has made this alternative more attractive to the formulation scientist. Eudragit RL PM and RS PM are just two examples of the many polymers designed for use in controlled-release matrix tablet formulations (9-15). The characterization of compressed tablets with regard to tensile strength may be helpful in explaining or predicting their dissolution profiles.

Tensile strength data provide basic information in the understanding of the compaction properties of compressed powders. Such data have been used widely in the pharmaceutical field, including formulation optimization (16), evaluation of direct compressibility of powders (17), the characterization of deformation, bonding, and capping behavior for single components (18) as well as binary mixtures (19), and the evaluation of coated tablets (20) and brittle materials (21).

Tensile strength is defined as the force (per unit area of broken face) required to split a powder compact (22). The correlation of tablet hardness (i.e., tensile strength) with compaction pressure is one of the most common methods of interpreting powder compaction data, and a variety of different techniques are described in the literature. The method employed herein is designed to evaluate the tensile strength of various blends of powders compressed into uniformly shaped square compacts. They were tested under conditions which minimize extraneous effects (such as tablet press compression rate and duration, punch shape and size variations, ejection force effects and variations between tensile testing equipment) (1). This leads to a more accurate assessment of the true tensile strength of the compact (23).

Several researchers have addressed the effects of different variables on the tensile strength of powders and compacts, including powder density, particle size distribution, and interparticular forces (24), plastic flow (25), moisture (26), particle size fractions (27), compressional force, concentration of binder, and aging (28), particle shape (29), crystal habit (30), melting point (31), and precompression force (32). Tensile strength data can be related to particle-particle interactions and true areas of contact (33) and compact porosity (34). Tablet tensile strength and lower punch work may be used together to determine the utilization of the energy of compaction (35). The ratio of tensile strengths of compacts with and without a small stress concentrating hole has been used to quantify the brittleness of materials (1,36). Nadai (37) discussed the general principles concerning the theory of tensile testing and related areas.

Previous reports (8,10,38,39) have addressed the dissolution properties of formulations for controlled-release matrix tablets containing Eudragit acrylic resin polymers. The objective of the present study is to evaluate some of the basic physical-mechanical properties of binary blends of acrylic resin copolymers and pharmaceutical compounds. This investigation is performed using equipment designed to eliminate or minimize factors that could lead to variablity of results and allows for an absolute comparison of tensile strengths of compounds to each other and, eventually, to other properties of the compacts such as the dissolution rate of the drug in the compact.

METHODOLOGY

The Eudragit acrylic resin polymers were obtained from Röhm Pharma, GmbH, Weiterstadt, West Germany. Theophylline and sodium sulfathiazole were obtained from Sigma Chemical Company, St. Louis, Mo. Blends were prepared in concentrations ranging from 20% drug to 80% drug and were mixed for 15 minutes in a twin shell V-blender (Patterson-Kelley Co., Inc., East Stroudsburg, PA). The pure drugs and

polymers alone were compressed into compacts and the tensile strengths were determined. All materials were passed through a 30 mesh sieve before mixing. Compacts were made using a Carver® 20 ton laboratory press modified with a load cell (I.S.I., Inc., Round Rock, TX) for measurements up to 10,000 kg for the compression of compacts, and up to 2000 kg for the tensile testing of the compacts. The strain gauge display unit allowed switching between these two ranges. The equipment used is based upon that of Hiestand and Smith (1) as modified by Williams and McGinity (40). The signal from the load cell on the press was monitored with a digital oscilloscope (Model 206-2 Explorer II, Nicolet Instrument Corp., Madison, WI). Each of the samples was compressed with a force sufficient to result in a solid fraction of 0.81 for the compact. Solid fraction is defined as one minus the porosity and is the apparent density divided by the true density. Trial and error was necessary to obtain the initial compression force required, based on the true density of the powder (or mixture) and the final volume of the compacts. True densities for each of the powders were determined with a helium pycnometer (Model 1302, Micromeritics Instrument Corp., Norcross, GA). The average of three samples was used.

Square compacts for tensile testing measured one inch on a side and weighed five grams. These were compressed in a split die allowing triaxial decompression in order to avoid the problems of capping or lamination at higher compression forces. Two sets of compacts for each material or blend were made in this study: one set of four compacts with a one millimeter axially oriented hole located in the center of the compacts and another set without the hole. Both halves of the aluminum die and each of the sets of square punches were coated with a non-stick Tufram® surface (General Magnaplate Corp., Arlington, TX) as described in detail in a previous study (40). One punch contained a spring loaded retractable one millimeter diameter pin for making the sets of compacts with the stress concentrating hole. All surfaces were coated with an ethanol/water slurry

of magnesium stearate which was allowed to dry prior to compression to help minimize sticking.

Tensile testing was carried out on the Carver press. Modification included a variable speed motor (Havatec Inc., Austin, TX) for driving the lower platen at a controlled rate of load application. Since many drugs and excipients are viscoelastic materials, their tensile strength is a time dependent process. Thus, it is important that the testing rate be carefully maintained at a constant value in order to minimize rate-dependent variations. This was accomplished by maintaining an arbitrarily chosen time constant of ten seconds between the maximum force (at the time of tensile failure) and 1/*e* (where *e* is the the base for the natural logarithm) times that value. If necessary, changes in the time constant were made by varying the speed of the motor driving the lower platen.

Compacts were centered between the upper and lower platens (measuring 0.4 times the width of the compacts) of the press and compressed transversely until tensile failure, indicated by a clean break into two equal halves, occurred. Tensile strengths were then calculated based on the maximum force recorded on the oscilloscope at failure. The brittle fracture index, which is based upon the ratio of the strength of compacts without a stress concentrating hole to that of compacts with such a stress concentrator, will be discussed in a future paper, along with the other tableting performance indices for the materials described in this manuscript.

RESULTS AND DISCUSSION

All results for tensile strength are reported as N/cm^2 versus the percentage of drug in the polymer. Figure 1 shows the results for the five acrylic resin polymers in combination with sodium sulfathiazole. A comparison of pure sodium sulfathiazole with values for each of the pure polymers reveals that compacts made from the pure drug are stronger than those made from the two methacrylate ester copolymers (Eudragit RL PM

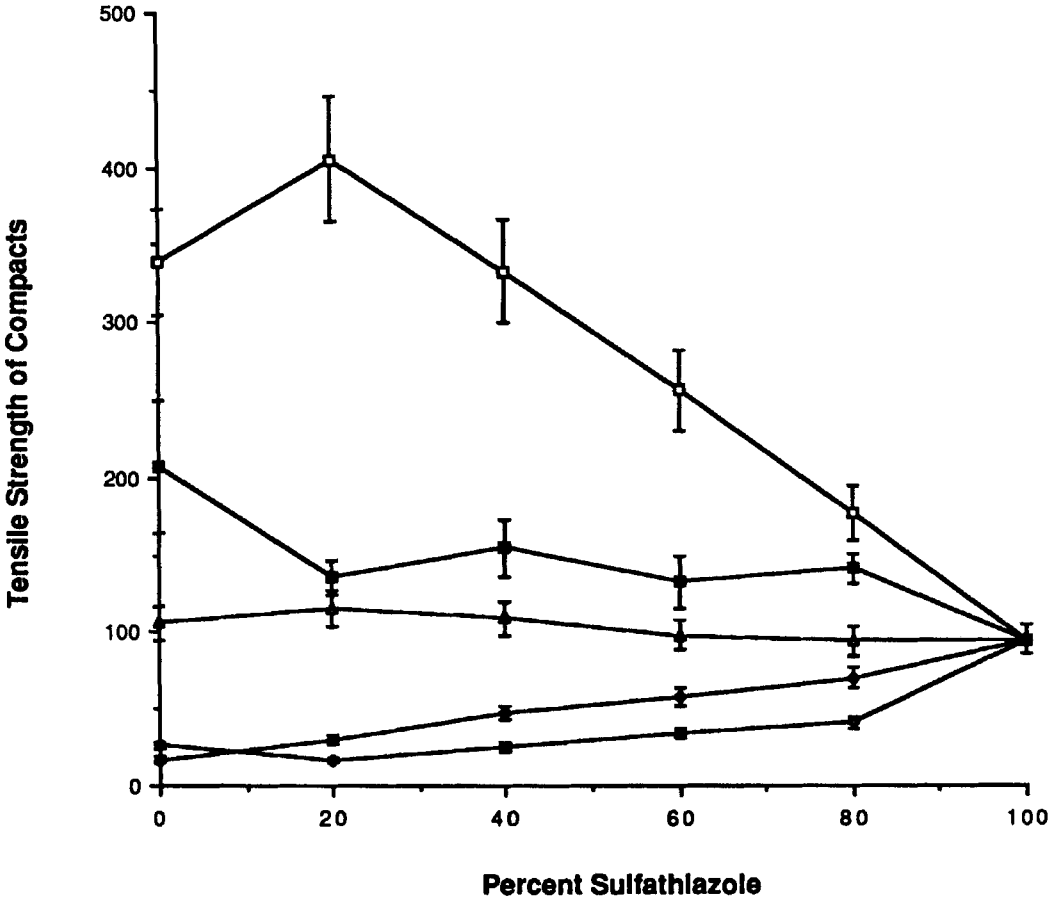

Figure 1

Tensile strengths of sodium sulfathiazole-Eudragit compacts. Key: (□) L 100-55; (■) L 100; (△) S 100; (◆) RL PM; (◇) RS PM.

and RS PM). Conversely, sodium sulfathiazole compacts are weaker than the methacrylic acid copolymer compacts (Eudragit L 100-55, L 100 and S 100). Sodium sulfathiazole, a brittle material, and the plastic compound, theophylline were chosen as model drugs. Approximately linear relationships exist between pure drug and pure polymer for these blends. One notable exception is seen with Eudragit L 100-55. For this polymer, a peak is observed at the 20% sodium sulfathiazole concentration, after which a linear drop in tensile strength to that of the pure drug level is seen. The significance of this peak lies in

the fact that it represents blends which show much higher tensile strengths than either of the two compounds from which they are formed. Reproducibility of tensile strengths for each of the compacts was good, with all standard deviations falling within ±10% for the average of four tests. Standard deviations are shown as error bars in all graphs.

Several trends with the polymers were observed. The methacrylic acid copolymers (Eudragits L 100-55, L 100, and S 100) proved to be the strongest of the five polymers throughout this study. Their brittleness, as determined from the brittle fracture index, was significantly higher that the other Eudragit polymers, and will be the subject of a future report. The methacrylic acid copolymers have previously been reported to be relatively brittle (2). The methacrylate ester copolymers (Eudragit RS PM and RL PM) are equivalent in strength at values much lower than the other three copolymers for all drug blends studied. It should be noted that the methacrylic acid copolymers are spray-dried materials, whereas the methacrylate ester copolymers are prepared by milling. Figures 2 and 3 illustrate the physical differences between the milled and spray-dried Eudragit acrylic resin copolymers, respectively. Particle sizes, however, are roughly equivalent for the two methods of preparation. Spray drying has been shown to completely change the compaction properties of amorphous lactose (41), possibly due to an increase in the consolidation due to plastic flow. Changes in crystal structure have been reported resulting from the spray drying of disodium cromoglycate leading to polymorphic or amorphous drug forms (42). While abundant literature exists concerning the effects of milling on pharmaceutical powders, few comparisons have been made to spray-dried materials. Preliminary work performed in our laboratory suggests that the method of preparation (spray-dried vs. milled) of a compound can have a significant effect on the physical-mechanical properties of the resulting compacts.

The results for the sodium sulfathiazole and acrylic resin copolymer blends for compacts weakened when a stress concentrating hole was introduced into the compacts are shown in Figure 4. The tensile strength of compacts containing a hole acting as a

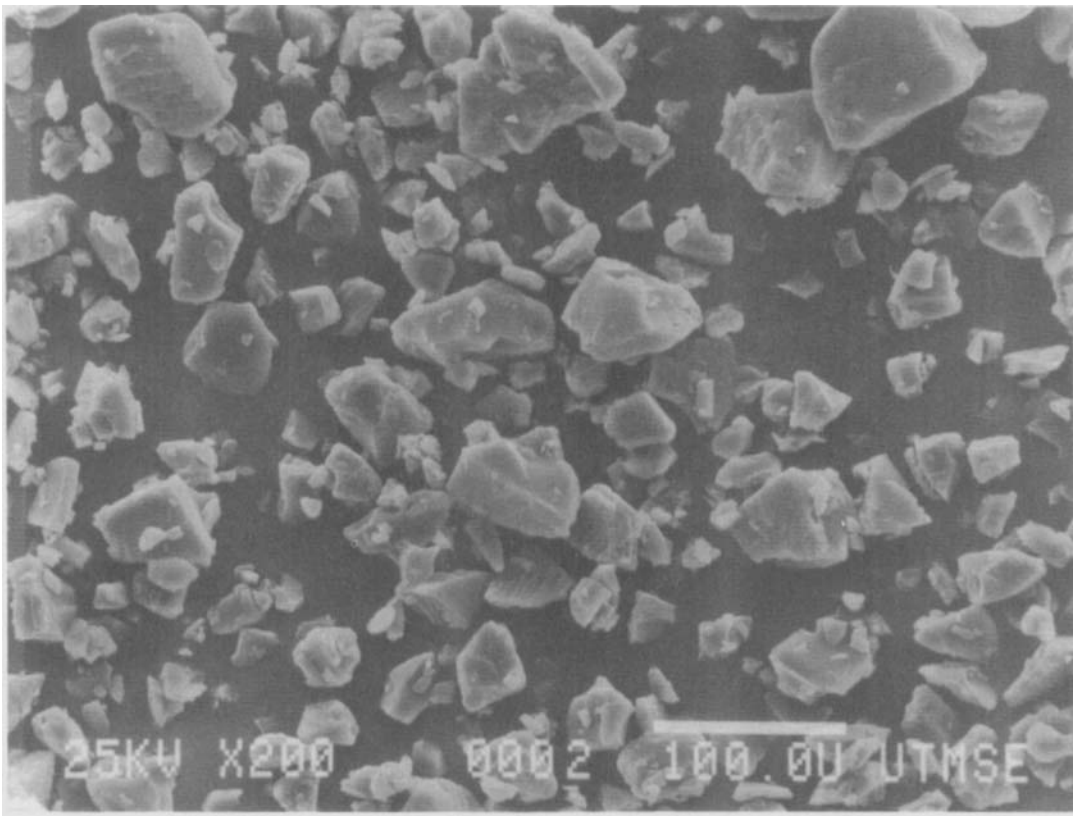

Figure 2

Scanning electron photomicrograph of Eudragit RS PM, representative of the milled acrylic resin copolymers.

stress concentrator is used to calculate the brittle fracture index (1). A similar set of tensile strength profiles as those in Figure 1 is seen, only on a smaller scale. Tensile strengths are decreased by more than 50% for all compacts containing the methacrylic acid copolymers which is an indication of the brittle nature of these substances. In Figure 4, it can also be seen that both Eudragit L 100-55 and L 100 show significantly higher tensile strength values for the blends when compared to either pure sodium sulfathiazole or the pure polymer alone. This could be due to more favorable intermolecular interactions between the drug and polymer. The approximately linear relationship is again seen with the two methacrylate ester copolymers throughout the range of concentrations.

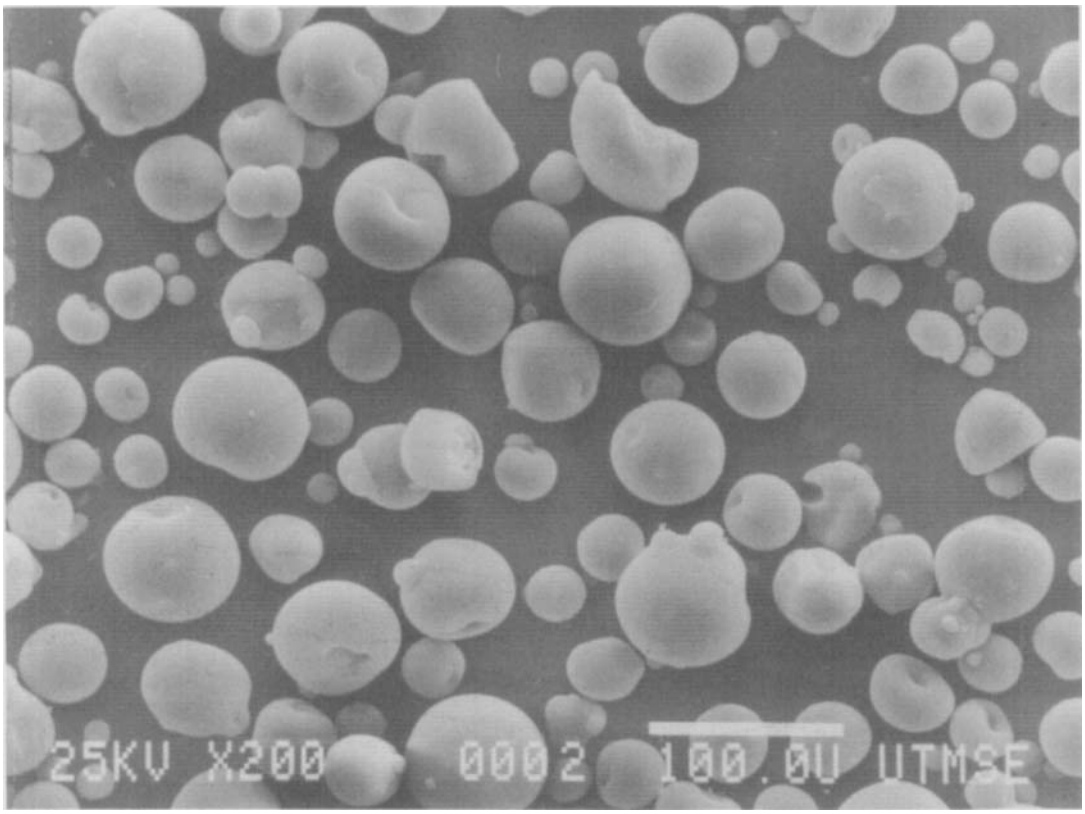

Figure 3

Scanning electron photomicrograph of Eudragit S 100, representative of the spray-dried acrylic resin copolymers.

In Figure 5, the tensile strengths for compacts consisting of blends of theophylline and each of the Eudragit polymers are illustrated. Profiles similar to the sodium sulfathiazole/polymer blends are seen with the theophylline blends. The differences between the two categories of polymers are even more pronounced with the theophylline-containing compacts. The Eudragit L 100-55 was shown to produce the strongest compacts, followed by Eudragit L 100 and S 100. All of the methacrylic acid copolymers exhibited much higher values for the blends (especially for the 40% and 60% drug concentrations) than the individual components alone. This was more apparent with theophylline than with the sulfathiazole blends, especially for the Eudragit L 100 and the

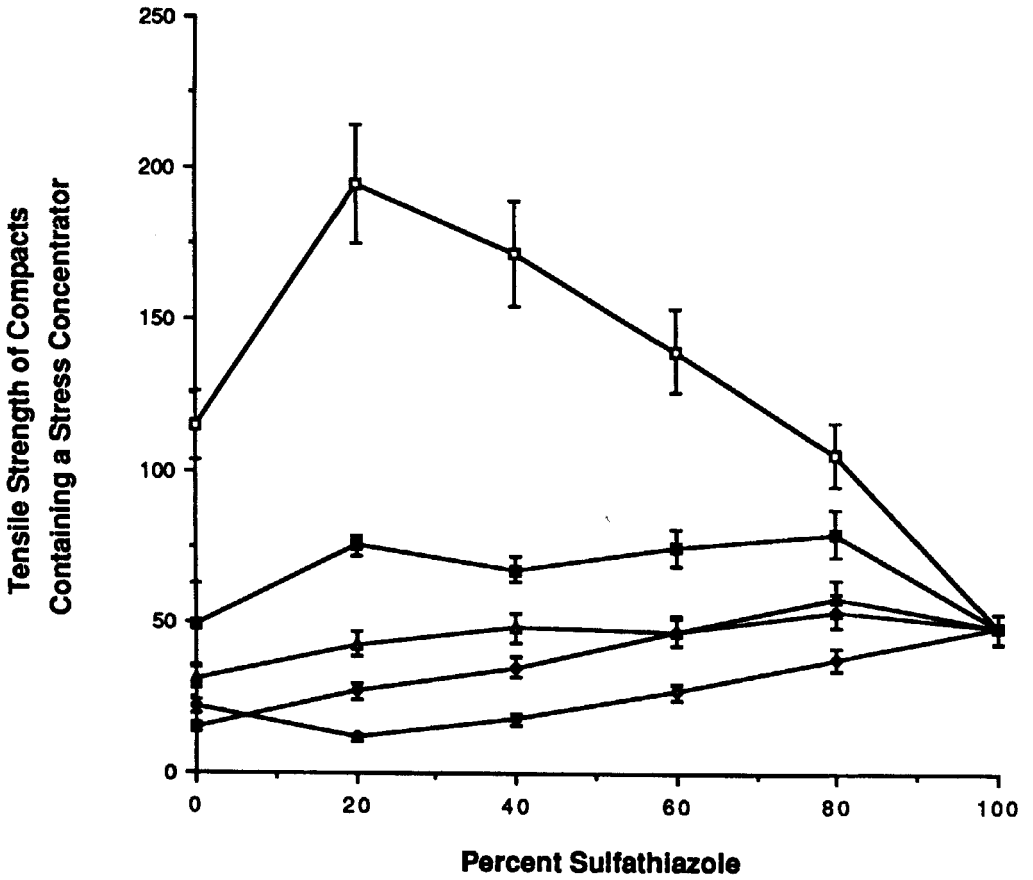

Figure 4

Tensile strengths of sodium sulfathiazole-Eudragit compacts containing a stress concentrator. Key: (□) L 100-55; (■) L 100; (△) S 100; (◆) RL PM; (◇) RS PM.

S 100. The two methacrylate ester copolymers (Eudragit RL PM and RS PM) follow theoretically predicted tensile strengths based on their relative composition, and are much weaker than their methacrylic acid copolymer counterparts.

Results for the corresponding compacts containing stress concentrators are seen in Figure 6. The plastic drug theophylline causes a smaller reduction in the strength of the combination compacts which were weakened with stress concentrators implying a decrease in their brittle nature. In addition to its increased strength when compared to

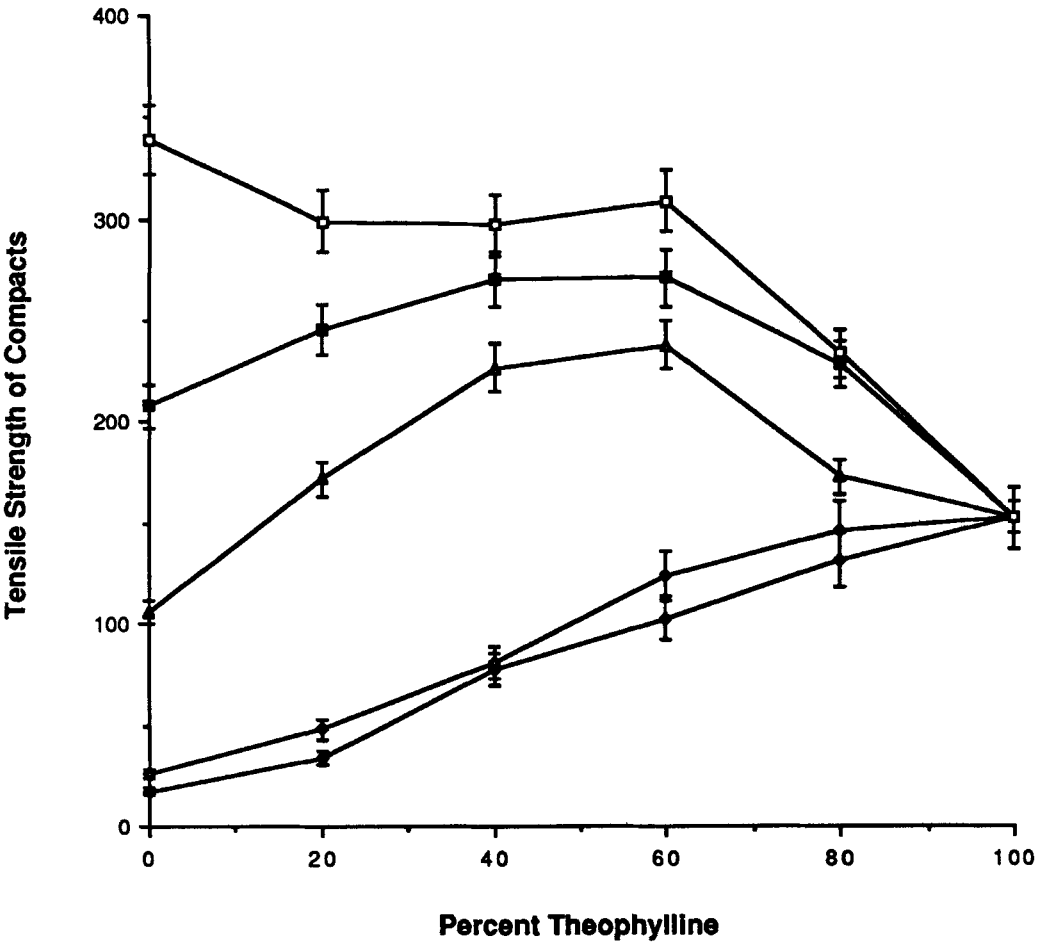

Figure 5

Tensile strengths of theophylline-Eudragit compacts. Key: (□) L 100-55; (■) L 100; (△) S 100; (◆) RL PM; (◇) RS PM.

sulfathiazole, theophylline is much less brittle, which supports previous tensile strength work performed in this laboratory. Compacts containing higher concentrations of the more brittle polymers (especially Eudragit L 100-55 and L 100) were of such high strength that when they did fail, the compacts shattered immediately after tensile failure. This behavior gave some indication of the strength and brittleness of the compacts at the higher polymer concentrations.

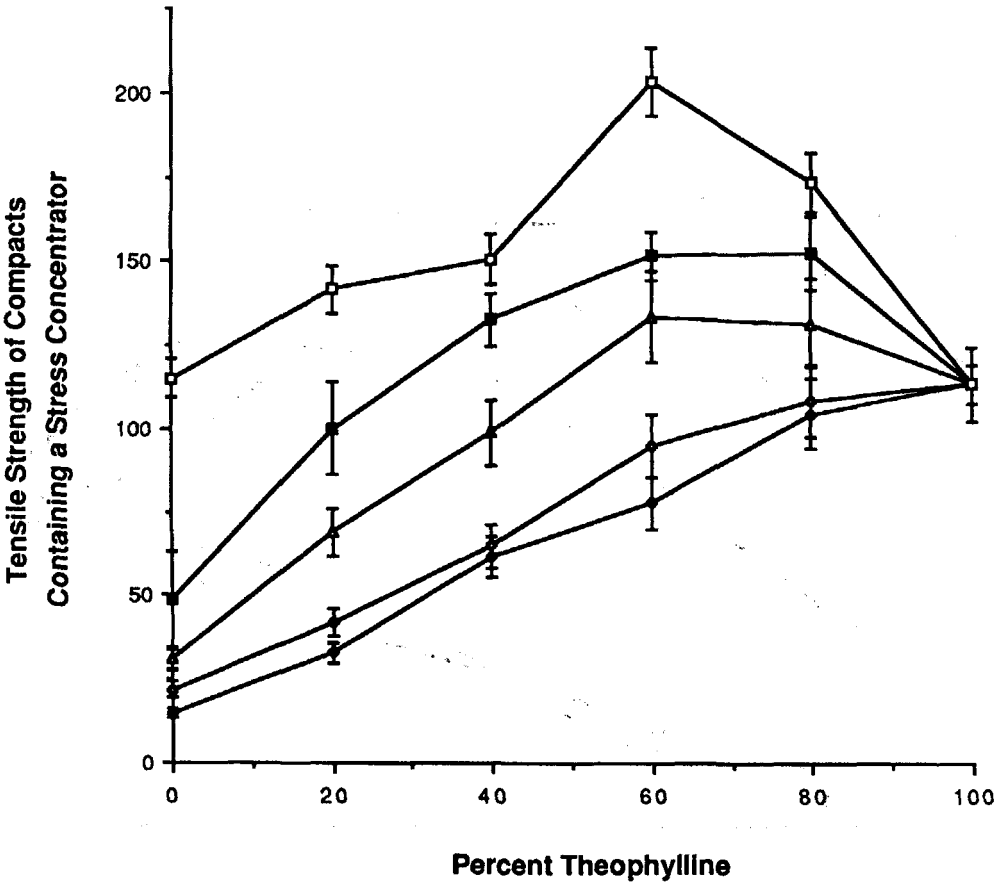

Figure 6

Tensile strengths of theophylline-Eudragit compacts containing a stress concentrator. Key: (□) L 100-55; (■) L 100; (△) S 100; (◆) RL PM; (◇) RS PM.

CONCLUSIONS

The methacrylic acid Eudragit copolymers displayed remarkably high tensile strengths. The Eudragit L 100-55 compacts were as strong as those of microcrystalline cellulose compacts compressed to the same solid fraction. Unlike microcrystalline cellulose, however, the Eudragit L 100-55 compacts were very brittle based upon a comparison of the strength of those compacts weakened with stress concentrating holes to those which were not weakened. This behavior is not as prominent at the lower (20%)

polymer concentrations. Most controlled-release oral dosage forms contain polymers at levels of 20% or less.

Several of the binary blend compacts showed higher tensile strengths than those of either of the components alone under similar conditions. This phenomenon could be attributed to a greater opportunity for drug-polymer hydrogen bonding to occur when compared to either drug-drug or polymer-polymer hydrogen bonding. At the pressures necessary to form a compact, an increase in the number of hydrogen bonds formed will significantly affect the strength of the resulting solid. Such bonds have been suggested as one of the mechanisms (together with extensive plastic flow) contributing to the favorable binding and compaction behavior of microcrystalline cellulose (3). A better fit for certain ratios of drug-to-polymer concentrations with packing and reinforcement of the polymer by the much lower molecular weight drugs may also improve the ability of hydrogen bonding to occur in these blends. Ongoing studies include experiments designed to support these hypotheses using X-ray diffraction and differential scanning calorimetry.

Mixtures of drugs with Eudragit methacrylate ester copolymers (RL PM and RS PM) generally followed patterns distinct from those of the methacrylic acid copolymers. The former were weaker, but were also much less brittle. Distinctions were greatest for the blends with the lowest concentrations of drugs. At low polymer concentrations (such as might be used in sustained-release oral dosage forms) the differences were still significant, but not nearly as great as those seen with the polymers alone.

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