DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(7), 753-779 (1995)

RESEARCH PAPERS

COMPACTION PROPERTIES OF SPHERONIZED BINARY GRANULAR MIXTURES

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ABSTRACT

Two spheronized granular formulations containing 20% anhydrous lactose/80% microcrystalline cellulose (MCC) and 80% anhydrous lactose/20% microcrystalline cellulose were blended in various proportions and compressed. Physical-mechanical properties of the resulting compacts were investigated using tableting indices and compared with powder mixtures of the same compositions. The compacts were compressed at a solid fraction of 0.80 for both powder and bead mixtures. An additional set of bead compacts were made at a solid fraction of 0.87. The thickness of the compacts was measured in the post-ejection stage to investigate their expansion behavior. The tensile strength with and without a stress concentrator and the dynamic indentation hardness of the compacts were determined. The brittle fracture index (BFI) and bonding index (BI) values were also calculated. The microstructure of the beads and compacts were investigated using scanning electron microscopy to observe the bonding phenomena. The results showed that the compacts made from beads underwent different

compaction/consolidation behaviors than the powders of the same lactose/MCC compositions. For powdered compacts, the tensile strength with or without a stress concentrator increased with increasing MCC content while the compacts made from beads showed the opposite trend. However, this trend was not seen in the indentation hardness test. The resulting BFI values were all low due to the plastic nature of the materials selected. The BI values of the bead and powder compacts also exhibited opposite tendencies and reflected the divergent mechanical properties of the materials presented in granulated and powdered forms. Microstructure studies revealed the bonding states between the beads in the compacts. Discrepancies in mechanical properties were related to the compressibility, compactibility, and porosities of the excipients studied.

INTRODUCTION

Granulations prepared by extrusion/spheronization have recently attracted extensive attention due to their potential controlled release applications, ease of handling, and high drug loading. The granulation process may yield beads with inter-/intraparticle voids, interparticle contact areas and morphologies that are significantly different from the powders from which they are made. Spheronization provides beads with rather smooth surface textures and homogeneous particle shapes compared to those made by traditional granulation methods. Spheres display diverging consolidation and deformation characteristics during compact formation as well as different mechanical properties or fracture mechanisms during compact testing. Elucidating the role that these parameters impart to compact properties will establish an important criterion for successful tablet formation using beads as excipient and/or drug carriers.

Many studies have been reported on the compaction of granules prepared by slugging or wet massing techniques. Alderborn et al. (1) and Wikberg et al. (2-4) reported that the degree of fragmentation propensity of the granules was an important factor for tablet strength and may be related to the precompaction granule porosity. Healey et al. (5) concluded that the effect of the granule porosity was not important except at low pressure. The influence of other parameters, including the homogeneity of binder distribution (6), the particle size of powder and binder

properties (7), binder concentration (8), granule size (9), granule structure (10) and the granulation method (11), has also been investigated. Other researchers have investigated the properties and strength of granules and their relationship to compact properties and/or strength (12-14). However, only limited work has been reported on the compaction of spheronized granules (15-18). Two tableting indices, bonding index (19) and brittle fracture index (20), have been successfully used in the evaluation of the elastic and plastic/brittle deformation characteristics of pure pharmaceutical ingredients, excipients (19, 21-23) and mixtures (24-27). These indices have also been used to predict capping and lamination tendencies in the compaction process. The objectives of the present study were to investigate the physical-mechanical properties of binary spheronized granular mixtures of anhydrous lactose and microcrystalline cellulose using the tableting indices. The compaction behaviors of these spheronized beads were also compared to those of compacts prepared from powdered mixtures of the same compositions.

METHODS AND MATERIALS

Materials:

Two spheronized granules made by extrusion/spheronization were used for this study: bead A, composed of 80% anhydrous lactose (Lactose DT)/ 20% microcrystalline cellulose (Avicel® PH 101) (MCC) and, bead B, composed of 20% anhydrous lactose/ 80% microcrystalline cellullose. The particle size of the beads ranged from 16 to 20 mesh. The anhydrous lactose and MCC powders from which the beads were made were obtained from Sheffield Products, Norwich, NY. and FMC Corp., Princeton, NJ, respectively. The powders were sieved to collect the 100 to 200 mesh particles for this study. All samples were equilibrated in an oven maintained at 40% R.H. and 25°C for at least three days prior to compaction to minimize the influence of humidity. Seven ratios of the bead and powder mixtures containing the same components were prepared: bead A/bead B=1/0, 5/1, 2/1, 1/1, 1/2, 1/5 and 0/1. The resulting compositions of both bead and powdered compacts were as follows: anhydrous lactose/MCC=80/20, 70/30, 60/40, 50/50, 40/60, 30/70 and 20/80. Compacts were also prepared from the pure anhydrous lactose and MCC powders alone, and their properties were investigated and

compared with published values. The powdered mixtures were blended using a V-blender for 30 minutes before equilibration. Each two gram bead mixture was individually weighed and equilibrated, then transferred into 20 mL glass containers and blended by hand for 30 seconds prior to compaction.

Compaction:

The equipment and the procedures used to make compacts were previously described (23). The blended samples were compressed using a Carver 25 ton laboratory press (Fred Carver Company, Menomonee Falls, WI) equipped with a load cell and LCD display (ISI, Inc., Round Rock, TX) to monitor the compression force needed to obtain the desired solid fraction. The compacts were made using 0.75 inch square tool steel punches and a split die to allow for triaxial decompression. In the present study, however, the press was modified to obtain better reproducibility. A cap was designed to be placed between the upper punch and the load cell to concentrate the compressive force at the center of the powder/bead beds (Fig. 1). Some compacts were prepared with a stress concentrating hole using an upper punch with a spring-loaded retractable pin. The time at the maximum compression pressure was held constant at an interval of one minute. At least 10 compacts were made for each group of measurements. All compacts were equilibrated at 40% R.H./ 25°C for at least 24 hours before the test.

Solid Fraction (SF):

The solid fraction of the compacts was determined using the following equation:

$$SF = \text{Apparent Density of Compact} / \text{True Density}$$

True density (excluding open and closed pores) was determined using a helium pycnometer (Model 1330, Micromeritics Corp., Norcross, GA). The powder particles were sieved to collect the fraction smaller than 200 mesh. The beads were ground using a jar mill (U.S. Stoneware Corp., East Palestine, OH) then passed through the same size sieve prior to measurement. The apparent densities of compacts were obtained from the ratio of the weight to the volume which was determined using a digital micrometer. The solid fraction of a set of compacts

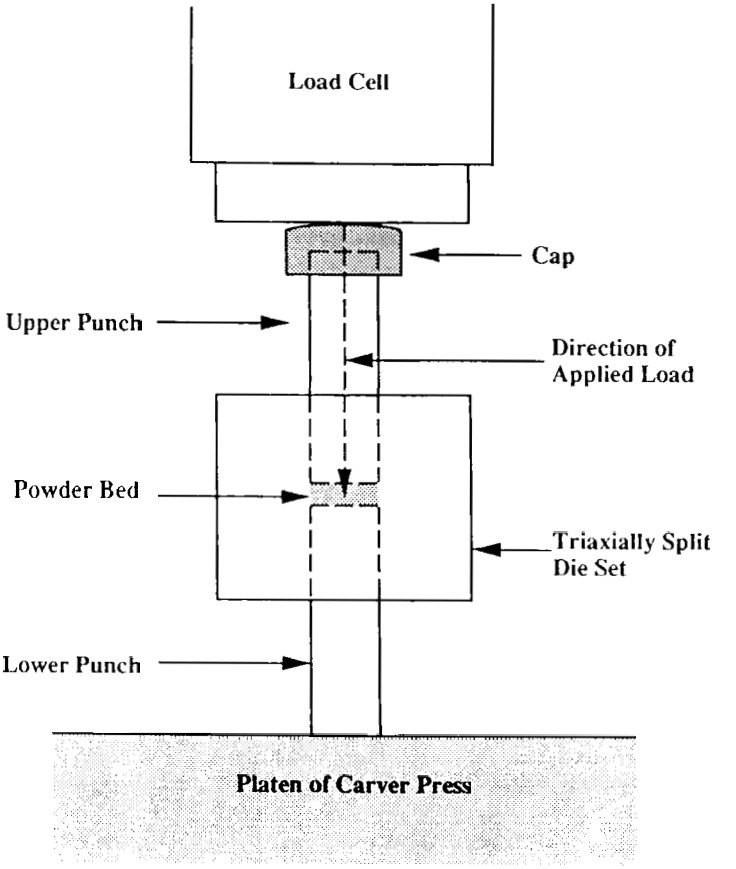

FIGURE 1

Schematic diagram of the load cell and the compaction unit used to concentrate the applied load.

prepared from either powders or beads was held at values between 0.78 and 0.80. An additional set of compacts was prepared from beads with solid fractions between 0.865 and 0.875.

Apparent particle densities of the beads (excluding open pores but including closed pores) were also determined as received using the helium pycnometer. The difference between true density and apparent particle density is the intragranular

porosity, while the difference between unity and solid fraction is the total porosity of the compact.

Tensile Strength (TS and TS_0) and Brittle Fracture Index (BFI):

An Instron universal tester (Model 4201, Instron Corp.) was used to measure the force needed to fracture a compact with and without a stress concentrator. The transverse compression method in which only the central 40% of the width of the compacts was covered by the platens was used (28). The tensile strength was obtained from the following equation:

$$TS \text{ (or } TS_0) = (0.16F)/(0.4WTh)$$

where F is the breaking force of the compacts, W is the side length, Th is the thickness of the compacts, and 0.16 is a constant derived from the photoelastic method (28). In this test, all the compacts had the same orientation, which was marked immediately after ejection from the die to minimize the effect of density gradients due to the nonuniform distribution of compression pressure (29). The displacement rate was set at 10 mm per minute all through this study. However, some compacts were fractured at the platen edge and the breaking strength for such compacts was not used to calculate the tensile strength.

The brittle fracture index was derived from the following equation:

$$BFI = [(TS/TS_0)-1]/2$$

where TS is tensile strength and TS_0 is tensile strength with a stress concentrator. Since the TS and TS_0 values were obtained from two independent groups of measurements, the standard deviation of the BFI values were derived via error propagation (30).

Indentation Hardness

The dynamic indentation hardness (P value) was evaluated using a pendulum test apparatus (31). The apparatus used in this study had been modified by Williams and McGinity (25) to include a ballistic sensor that was capable of accurate and reproducible measurement of the inbound and rebound velocities of the indentor

before and after impacting the compacts. The chordal radius of the contact area, produced by a steel spherical indenter, was measured under an optical microscope (Zeiss Corp., Germany) using a stage mounted micrometer.

The inbound velocity (V_i), rebound velocity (V_r) and the chordal radius were then used to calculate the indentation hardness (P) as expressed in the following equations:

$$P = (4\ mgrh_r/\pi a^4)[(h_i/h_r)-3/8]$$

where m is the mass of the indenter, g is the gravitational constant, r is the radius of the idenier, a is the chordal radius, h_i is the initial height of the indenter and h_r is the rebound height of the indenter, which are derived from V_i and V_r, respectively.

The tensile strength and indentation hardness were used to calculate the bonding index by the following equation. The standard deviations of BI values were obtained through error propagation of TS and P data.

$$BI = TS/P = \text{Tensile Strength/Indentation Hardness}$$

Percentage Elastic Recovery (%ER)

The thickness of the compacts immediately after ejection (T_i) from the die and after a 24 hour relaxation period (T_r) was measured using a digital micrometer to obtain the percentage elastic recovery (%ER) values of the post-ejection stage as follows:

$$\%ER = [(T_r - T_i)/T_i] \times 100$$

RESULTS AND DISCUSSION

The binary granular mixtures are heterogeneous anisotropic systems. They may be considered to be two-phase particulate composite materials, where a relatively small quantity of one solid material is dispersed in a second solid material acting as the continuous matrix. The presence of the dispersed phase may alter the plastic/brittle characteristics of the continuous phase due to the stress localization effect and the properties of the dispersed phase. The compaction properties of the

TABLE 1

Densities and Porosities of Lactose-rich Bead (Bead A) and MCC-rich Bead (Bead B).

	T. D.	A. P. D.	E. I. P.
Bead A (Lactose / MCC = 80 /20)	1.5563	1.5384	1.15
Bead B (Lactose / MCC = 20 / 80)	1.5480	1.4819	4.27

T. D. = true density, A. P. D. = apparent particle density, E. I. P. = estimated intragranular porosity

mixture may still be dominated by the continuous phase. However, the overall integrity of such systems rely on the composition, particle size, strength, compressibility/compactibility of both phases, the proportion and the distribution of one phase in the other and the bonding compatibility between the two. The number of the parameters makes quantitating the individual contribution of each factor impractical. To simplify this complexity, the beads were treated as single entities rather than as mixtures since the individual ingredients did not clearly exhibit their primitive physical properties as they were embedded in the beads through the granulation procedures. It was also assumed that the compacts were statistically homogeneous, i.e., any small portion extracted from the material had the same properties as the entire sample.

The porosities of granules prepared by extrusion/spheronization processes are related to the spheronization speed, the drying process (32), the particle sizes of materials used and the amount of water added (33). As shown in Table 1, both bead formulations selected for this study displayed low porosity values.

In compaction studies using granules made by wet massing-screen procedures, Wikberg and Alderborn (2,4) proposed that the increase in granule porosity might increase the degree of fragmentation propensity, i.e., the tendency for particles to break-down or collapse during the compression phase. This had previously been

shown to be important in the consolidation/deformation mechanisms for materials such as Emcompress®, saccharose and lactose (34) and the granulations from which they were made. However, the porosities of the granulations investigated for these excipients ranged from 11.6% to 31.3% and were comparatively higher than those of the two bead formulations in the present study. In the low range of porosity, bead B (MCC-rich bead) possessed a higher porosity than bead A (lactose-rich bead). Bead A, however, was much more compactible and compressible, using a compressive stress of 89 MPa versus 160 MPa for bead B to reach a solid fraction of 0.80. Compactibility has been defined as the ability of a material to be compressed into a tablet of certain strength; compressibility has been defined as the ability of a material to reduce volume under pressure (35).

The viscoelastic properties of pharmaceutical substances were considered an important determinant in compaction. The Maxwell model, the Kelvin model (36), and their modifications have been employed to elucidate mathematically these characteristics. The elastic recovery, formerly defined as the magnitude of axial expansion of compacts at ejection relative to the their thicknesses under maximum pressure, is an indirect approach for measuring the disruptive effects of instantaneous elastic deformation during the decompression stage, and has been employed by several workers (37, 38). In our study, the time interval for dimensional expansion measurements was selected to signify the time-dependent recovery which a compact slowly undergoes at zero stress in the post-ejection stage, a phenomenon generally regarded as a viscoelastic behavior (39-41). The time to reach equilibrium is, however, material and temperature-dependent. Several approaches, including a stress relaxation test under constant strain (42-44), a creep test under constant stress (45), and the difference between the bonding indices derived from fast and slow-acting indentation hardnesses (47) have been employed to investigate the viscoelasctic behaviors in bond formation during compaction. The objective of the elastic recovery test in the present study was to describe qualitatively the viscoelastic characteristics of the material selected rather than evaluate its viscoelastic properties in bonding. A 24-hour period under constant humidity and temperature was selected in this study for complete relaxation to occur.

Table 2 shows a comparison of the percentage of elastic recovery (%ER) values of the compacts composed of beads and of the powder mixtures. Both compacts

TABLE 2

Percentage Elastic Recovery of Compacts Made of Bead A, B and Two Powder Mixtures of the Same Compositions at Two Solid Fractions.

	% ER	S. D.	n
Bead A (SF = 0.80)	0.66	0.15	28
Bead A (SF = 0.87)	0.45	0.01	10
Powder (SF = 0.80), Lactose / MCC = 80 / 20	0.53	0.16	27
Powder (SF = 0.87), Lactose / MCC = 80 / 20	0.64	0.07	11
Bead B (SF = 0.80)	1.40	0.27	21
Bead B (SF = 0.87)	2.32	0.31	12
Powder (SF = 0.80), Lactose / MCC = 80 / 20	1.55	0.21	34
Powder (SF = 0.87), Lactose / MCC = 80 / 20	1.24	0.13	10

% ER = percentage elastic recovery, S.D. = standard deviation, n = number of measurements.

made from the MCC-rich powder mixture and MCC-rich beads showed significant viscoelastic expansion after ejection from the die. Lower values were found for the lactose-rich powder mixture and lactose-rich beads. The %ER of the MCC-rich bead compacts made at the solid fraction of 0.87 was higher than that from compacts of solid fraction 0.80 and lower for compacts prepared from powders with the same lactose/MCC composition. The energy derived from higher compression stress, at the solid fraction of 0.87, could be predominantly consumed

by the bond formation via irreversible plastic deformation of MCC-rich powder mixture. Less residual energy was released by elastic/viscoelastic expansion. This observation agrees with results reported by Krycer et al. (48). The compacts of lactose-rich powder mixture, being similar to most other pharmaceutical materials, exhibited a higher disruptive effect at higher pressure due to its less plastic nature, while the bead compacts displayed different behaviors. To a lesser degree, the force used to compress the MCC-rich beads created bonds due to the beads' minimal compressibility and compactibility. The remaining compressive energy, which was released as dimensional expansion for the compacts made at the higher solid fraction, was mainly reflected by a higher %ER value. Alternatively, the lactose-rich beads showed a tendency towards a lower recovery energy which indicated a decrease in viscoelastic properties. A lower %ER value was derived at the higher solid fraction, again, due to its relatively higher compactibility and compressibility. It has been suggested that elastic expansion was the result of bonds breaking in the compact instead of simply a reflection of the properties of the individual components (49). This might be true for powder compacts with homogeneous ingredients and void distribution, which are continuous, isotropic systems with mechanical behaviors that reflect the collective properties including bonding conditions. Alternatively, this behavior may represent the internal change of the beads based on the nature of the components, if those beads were compacted under a pressure which was not sufficient for bond formation at the intergranular contact points. The MCC-rich beads were such a case, being well-consolidated entities due to the strong bonding property of MCC. Weak bonds were formed between the beads under the compression pressure employed (160 MPa for solid fraction 0.80, 194 MPa for solid fraction 0.87). The difference in expansion properties of two materials are critical for binary bead mixtures. If the dispersed phase undergoes less expansion, they will be subjected to isostatic tension, and the matrix will be under radial tension and circumferential compression. Conversely, if the dispersed phase expands more than the matrix, the dispersed phases will be under isostatic compression, and the matrix will be exposed to radial compression and circumferential tension. Cracking may occur spontaneously before the system reaches equilibrium if these stresses are high enough to break the interparticle bonds (50).

The results of tensile strength (TS) and the tensile strength with a stress concentrator (TS_O) for compacts made from beads and powders are shown in

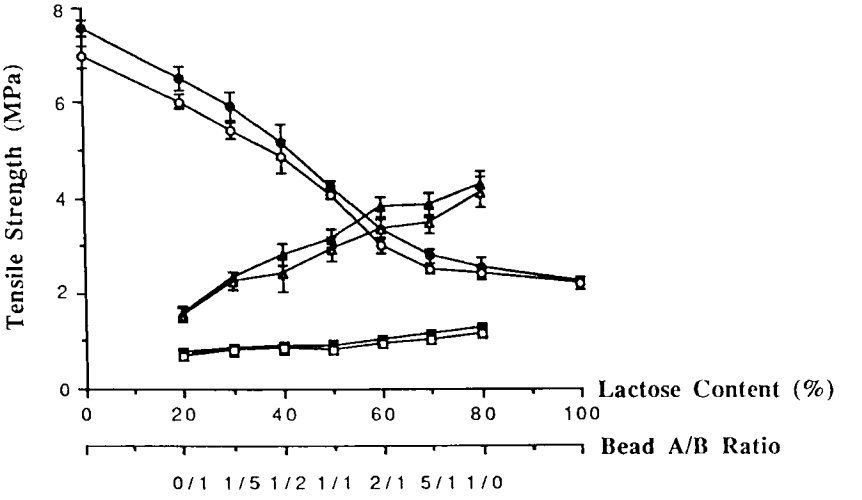

FIGURE 2

Tensile strength with (TS_O) and without (TS) a stress concentrator of compacts made from powders and beads as a function of anhydrous lactose content. Vertical bars represent standard deviations. Key: (●), TS of powder at SF=0.80; (○); TS_O of powder at SF=0.80; (■), TS of beads at SF=0.80; (□), TS_O of beads at SF=0.80; (▲), TS of beads at SF=0.87; (△), TS_O of beads at SF=0.87.

Figure 2. Tensile strength is generally regarded as resistance to fracture. The difficulty in this critical test lies in the highly anisotropic, heterogeneous characteristics and high interparticular voidage of the binary bead compacts, i.e., the cracks and the distribution of one bead formulation in the other. The low compactibility of the bead B formulation yielded a poorly connective material both in pure B compacts and in binary bead compacts. In this study, only the compacts made from the bead A/bead B ratios controlled at 2:1 and 5:1 showed intact appearance, and no apparent defects could be found at the edges of the compacts. In metallurgy, a maximum ratio of hard phase to soft phase has been suggested to be 30% by volume in binary metal aggregates so that the soft phase could form a continuous phase around the hard phase (51). In our results, a value of 33.3% (bead A/bead B=2:1) of bead B which was incorporated in the compacts to obtain acceptable mechanical strength was quite similar to the value suggested.

On the other hand, the narrow range of the particle size selected in this study yielded beads unable to deform in the same way as a powder blend, where small particles may occupy the interparticle vacancies in consolidation. As a consequence, the volume of the individual interparticle voids in the compacts are larger. However, whether flaws, cracks or voids are present, all can concentrate stress and increase tendencies to fracture prematurely under stress. Lower TS values will also be obtained. This stress concentration effect varies with the geometry of the cracks; i.e., a sharp crack severely concentrates stress (52). Furthermore, in our study, the crushing force varied with the distribution of two beads in the zones covered under the compression platen in this test as the ratio between the two bead formulations changed. Higher variance was observed for all of the bead compacts with the average values of coefficient of variation of 10.3% and 8% at SF=0.80 and 0.87, respectively, in comparison with 4.5% for powder compacts at SF=0.80. Nevertheless, poor bonding due to low compactibility were reflected by low tensile strength for the bead compacts at SF=0.80 (Fig. 2) and no clear trend in the mechanical strength with respect to the compositions was displayed. The more compactible bead A did not plastically deform to form strong bonds between the beads to create compacts with high strength. The improvement can be observed from the values of the compacts prepared at SF=0.87. Consequent to the higher compactibility of lactose-rich beads, the TS and TS_0 values increased as their content in the compacts increased. Alternatively, the TS and TS_0 values increased as microcrystalline cellulose increased for the compacts prepared from powder mixtures of solid fraction 0.80. Microcrystalline cellulose has been found to be a very effective binder due to its good compressibility, and the formation of hydrogen bonds in the compacts has been reported to be a critical contribution (53). The superior plastic property, compactibility, and low Young's modulus have been extensively reported (54-56). The incorporation of MCC into tablet formulation contributes significantly to the mechanical strength of the tablets.

The brittle fracture index indicates the ability or inability of the compacts to relieve stress by plastic deformation around the stress concentrating region in a compact. The BFI values calculated from TS and TS_0 data are displayed in Figure 3. All three sets of compacts made from bead and powder mixtures demonstrated a very low BFI values and no apparent relationship between BFI and the ratio of the components was obtained. The BFI value of 0.044 obtained for Avicel® PH 101 in the present study was similar to the values by other researches. Roberts and

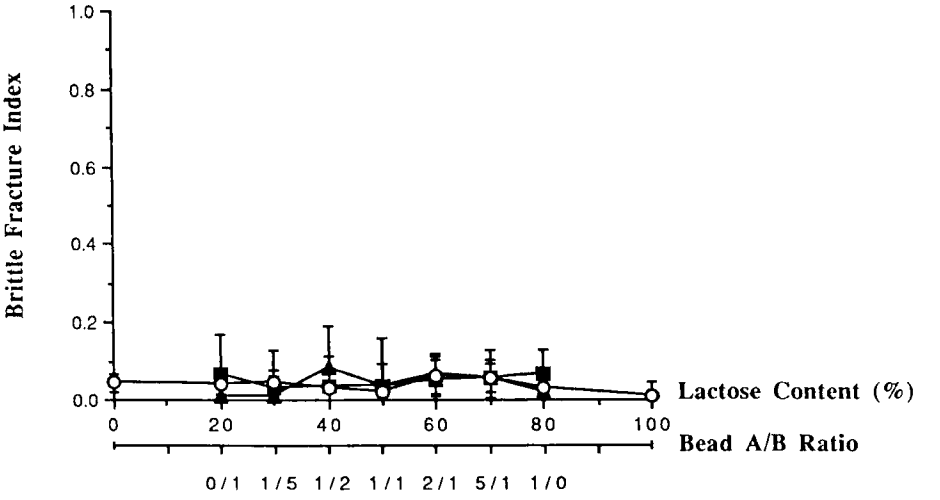

FIGURE 3

Brittle fracture indices of compacts composed of powders and beads as a function of anhydrous lactose content. Vertical bars represent standard deviations. Key: (○), powder at SF=0.80; (■), beads at SF=0.80; (▲), beads at SF=0.87.

Rowe reported brittle fracture propensity values of 0.083 and 0.055 for compacts compressed to a solid fraction of 0.75. The punch velocities were 3.33mm/sec and 200 mm/sec, respectively (21). Williams and McGinity obtained a BFI value of 0.1 for compacts with a solid fraction of 0.81 (26). Similar low values were obtained by Hiestand and Smith for Avicel® PH 102 (19). For powdered compacts, the low BFI values can be ascribed to the plastic characteristics of MCC and anhydrous lactose, even though MCC has been reported to be brittle at zero porosity (54) and anhydrous lactose has been reported to undergo fragmention under compaction pressure (57). For the compacts made from beads, the actual TS_0 values may be impaired by the intergranular voids at the two solid fractions selected, especially for the compacts of lower solid fraction. However, the solid fraction of 0.85 or 0.9 recommended by Hiestand and Smith (19) for powders might not be a suitable choice for beads due to the nonuniform distribution of interparticular voids.

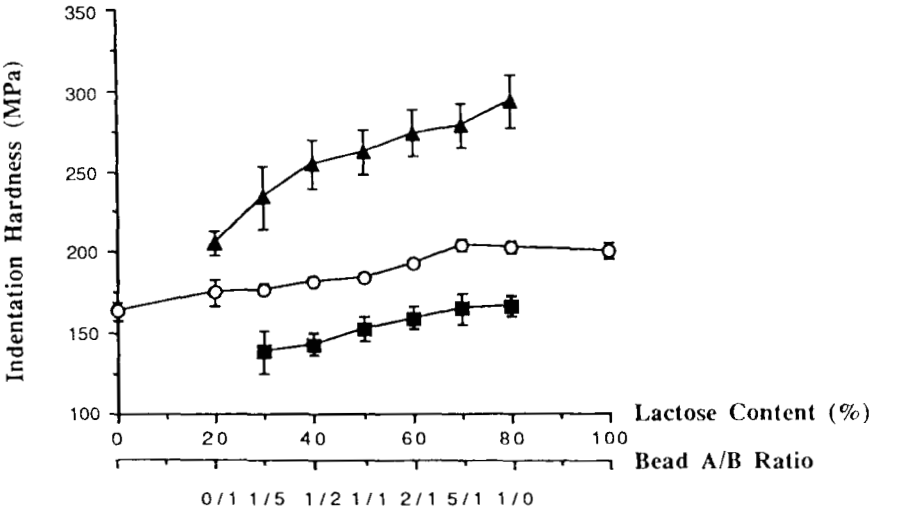

FIGURE 4

Indentation hardness of compacts composed of powders and beads as a function of anhydrous lactose content. Vertical bars represent standard deviations. Key: (○), powder at SF=0.80; (■), beads at SF=0.80; (▲), beads at SF=0.87.

The indentation hardness (P value) is regarded as the resistance of material to permanent deformation. The two indentation hardness tests that have been used include the Brinell hardness test and its modifications (46, 58), and the pendulum hardness test (31). The Brinell hardness test characterizes the slow-acting deformation including the time-dependent viscoelastic behavior, while the latter indicates only the instantaneous plastic flow (31). The pendulum hardness test was selected for this study and the results are shown in Fig. 4. The hardness increased as the lactose content in the powdered compacts increased. A similar tendency was seen for the compacts prepared from beads at both solid fractions. The higher hardness values of the compacts which contained more lactose-rich beads resulted from the higher compactibility of those beads, a phenomenon which was in accordance with Luenberger's theory of compactibility (59, 60). For the compacts of bead formulations, larger interparticle voids generated under lower compression pressure absorbed part of the kinetic energy from the inbounding sphere and the

distinction between each bead formulation was diminished. However, the overall tendency of the increase in hardness as lactose content increased was more dramatic for the denser compacts (i.e., SF=0.87) produced under greater pressure. From the viewpoint of continuum mechanics, the particles should be compressed to form macroscopically consecutive units such that the effect of particle size would be minimized. It has been suggested (60) that the decrease in particle size may be accompanied by an increase in hardness since the dislocations created by the indenter are impeded by the particle boundaries. This effect should be considered since the bead size and the dent size are virtually of the same order.

The bonding index is defined as the ratio of the tensile strength to the indentation hardness of a material at a specified solid fraction. To include the viscoelastic effect on bond formation, Hiestand and coworkers (46, 47) recently suggested a long dwell time indentation test using a motorized screw arrangement similar to a Brinell test apparatus. The bonding index obtained from this static indentation hardness test was termed " the best case" bonding index for the purpose of discriminating " the worst case " bonding index used in this study. Due to the anisotropic and heterogeneous nature of the binary bead formulations, only plastic deformation was taken into account for elucidation of the significance of the BI.

The profiles in Fig. 5 demonstrate the relationship between the BI and compact composition. Compacts made from beads at the solid fraction of 0.80 showed low BI values at each ratio investigated. However, the slightly higher BI values of the compacts with higher percentage of bead A demonstrated the survival of the intergranular contact surface after compression, due to the plastic and/or fragmenting nature of the granules with high lactose content. This tendency was more apparent for the compacts at SF=0.87. In Hiestand's theory of tablet bond formation, isthmus formation (19, 47) was a major mechanism which occurred during ductile extension at the interparticular contact zones. The larger isthmus regions which survived after ejection corresponded to high BI values and in turn corresponded to strong compacts. However, the isthmus formation through simple plastic deformation was related to particle size. It has been suggested (61) that, if the plastic deformation occurred, the unloaded, harmonic mean radius of the curvature of the two contacting spherical surfaces should be increased to be larger than the harmonic mean of the original particle radii. In other words, the particle radii should be smaller than some critical values (46), so that ductile extension

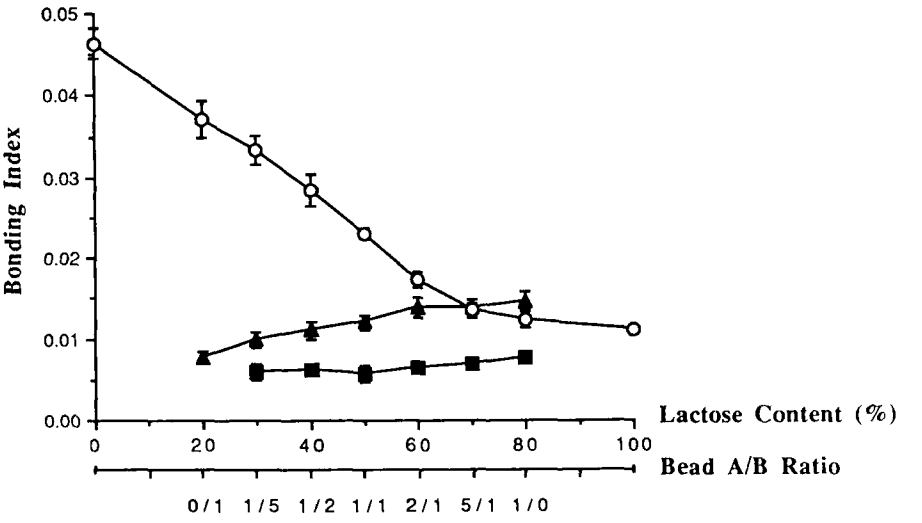

FIGURE 5

Bonding indices of compacts composed of powders and beads as a function of anhydrous lactose content. Vertical bars represent standard deviations. Key: (O), powder at SF=0.80; (■), beads at SF=0.80; (▲), beads at SF=0.87.

could take place. Two conditions were required for the isthmus formation via plastic deformation (assuming only plastic deformation was involved) after the yield point was surpassed and the magnitude of compression stress needed for deformation was reached. The first was that the frictional force, including particle-particle and particle-die, should exceeded. The second was that the compression stress was large enough to overcome the size effect. For beads, the first condition is less significant due to their smaller surface area, and the effect of particle size was considered to be a more important factor which hindered the isthmus formation.

The BI values of the compacts prepared from the beads at SF=0.80 were low. However, the presence of bonds may be questioned for the compacts composed mainly of bead B, since some individual bead B particles could readily be separated from the compacts. The same phenomenon was also observed at SF=0.87. Careful

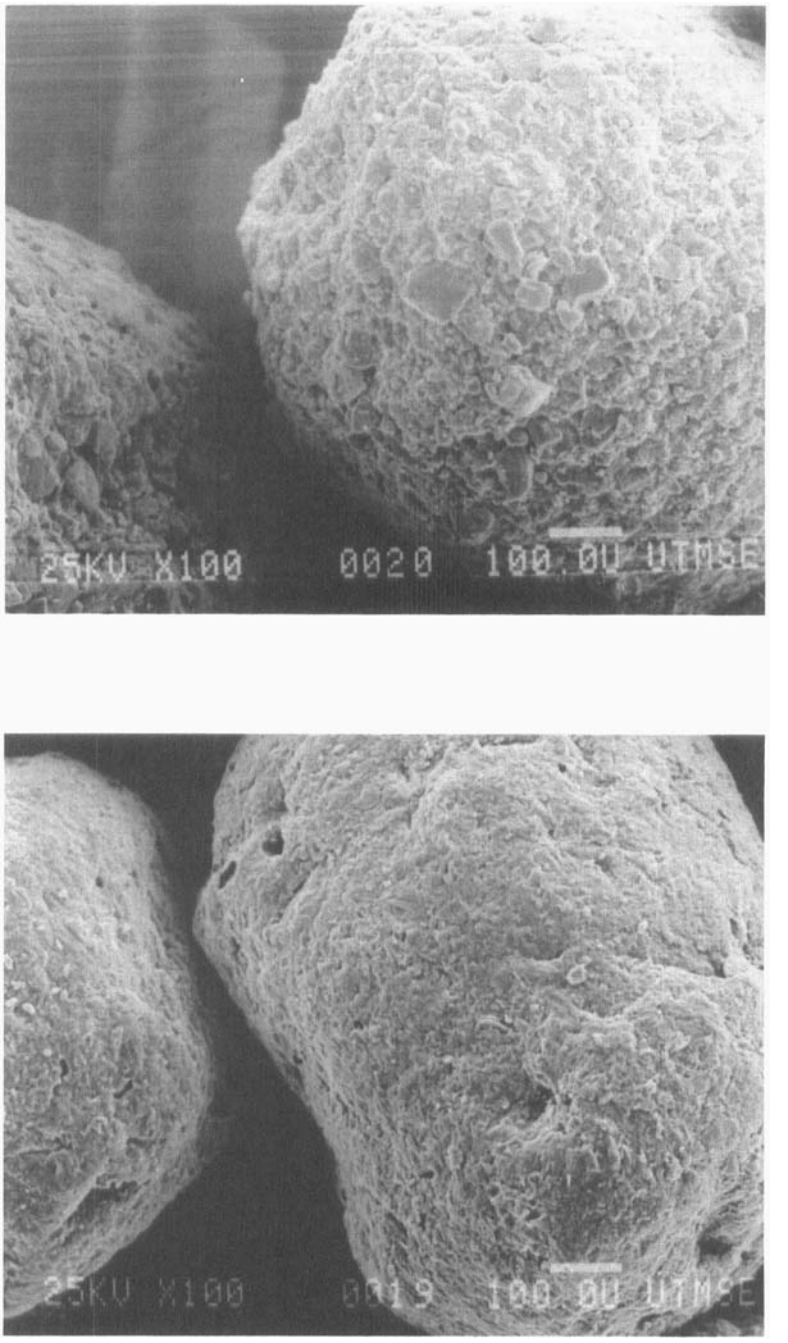

FIGURE 6

Scanning electron micrographs of the surfaces of beads. (a). Lactose-rich bead. (b). MCC-rich bead.

inspection revealed that the beads were not fragmented, but simply distorted. In these compacts, the compression pressure was increased to alter particle structure but contributed little to interparticle bonding, due to the poor compactibility of the beads.

Unlike the bead mixtures, the BI values of the powder compacts exhibited a positive relationship to Avicel® PH 101 content. This was attributed to the high bonding capacity based on the superior plasticity of MCC, which has been evaluated previously, using the same approaches to derive similar values (19, 24). Moreover, low Young's modulus was also found to confirm its good compressibility. A slight negative deviation from the interpolation linearity between two components was observed for the BI profiles. The negative interaction in compaction/consolidation was ascribed by Leuenberger et al. (35) to the higher affinity between like particles than that between unlike particles. In their study, one interaction term was introduced to the compressibility/compactibility formulas for better prediction of deformation properties. In contrast to the above assumption , Riepma et al. (62-64) suggested that there was no interaction between the ingredients with the same particle size fractions in the determination of crushing strength, though the cause was the decrease of fragmentation potential of the single particles due to the incorporation of the fine particles. However, due to the limited particle size range we selected and the minor role that cohesion/adhesion effect played in compaction, similar behavior was not observed for the compacts made from beads.

Using scanning electron microscopy (Fig. 6), it was observed that the surface of lactose-rich bead showed more flakes and was less smooth than the MCC-rich bead. The two bead formulations showed overall smoother surface textures than the granules made by wet massing methods. Such surface smoothness would be advantageous for fluidity and the application of a film coat, but detrimental to bond formation in the consolidation processes. However, some microcrystals deposited on the lactose-rich beads might be critical for bonding either by brittle fracture or mechanical interlocking. During powder compaction, particles were rearranged and distorted, then plastically deformed and/or fragmented to create new contact areas for bond formation. The molecular or atomic interparticular interaction such as cohesion or adhesion was regarded as the important mechanism for bonding. Mechanical interlocking has been regarded as a minor contribution in powder

consolidation (65), even though it has been suggested that the case of Avicel® PH 101 might be the possible exception (66). Nevertheless, mechanical interlocking may be the predominant consolidation mechanism for larger particles, and surface roughness and irregularity are the major factors determining this behavior by providing a larger degree of interparticle contact in compression (29). Furthermore, it was suggested (33) that for larger particles, interparticular interactions at the molecular level such as van der Waal forces were secondary to the frictional force between the particles, and the physical mechanical properties of the particles became more important in bond formation. Nevertheless, when the compression force is strong enough to break the beads into fragments, the interactions at the molecular level will become more important when the fragments are brought into close enough proximity to allow the interactions at the molecular level to occur.

For the two bead formulations selected in this study, the scanning electron micrographs show that the surface properties of the beads influenced the compact formation. The fracture surface of the lactose-rich bead and the transverse section surface of the MCC-rich bead were displayed in Fig. 7a and 7b, respectively. In the case of lactose-rich beads, the fracture surface was obtained by the crushing method, while it was difficult to fracture the MCC-rich beads using this method, so a scalpel was used to obtain the transverse section surface. The internal structures of both beads displayed low porosity consistant with the porosity data of Table 1.

The fracture surfaces of compacts showing the state of bonding conditions are displayed in Fig. 8. The compact made from bead B at SF=0.87 did not exhibit bond formation, and interparticular gaps are still visible (Fig. 8a). Some of the beads were fragmented, while others were distorted, but still remained intact and could be readily separated from the compacts. Much stronger consolidation was observed from compacts made of bead A and a tighter coherence is seen in Fig. 8b. No single bead granule could be separated from the compacts. The compacts made from binary bead mixtures displayed the adherence between the two bead formulations. Particles from the lactose-rich formulation were fractured when compressed and acted as a solid bridge between the MCC-rich beads which still remained intact under the same pressure (Fig. 8c). The poor compactibility of bead B was ascribed to the loss of plasticity of MCC during the wet granulation process. Staniforth and coworkers correlated the amount of water used in the granulation processes to the compaction properties of MCC (67, 68). However, the tough

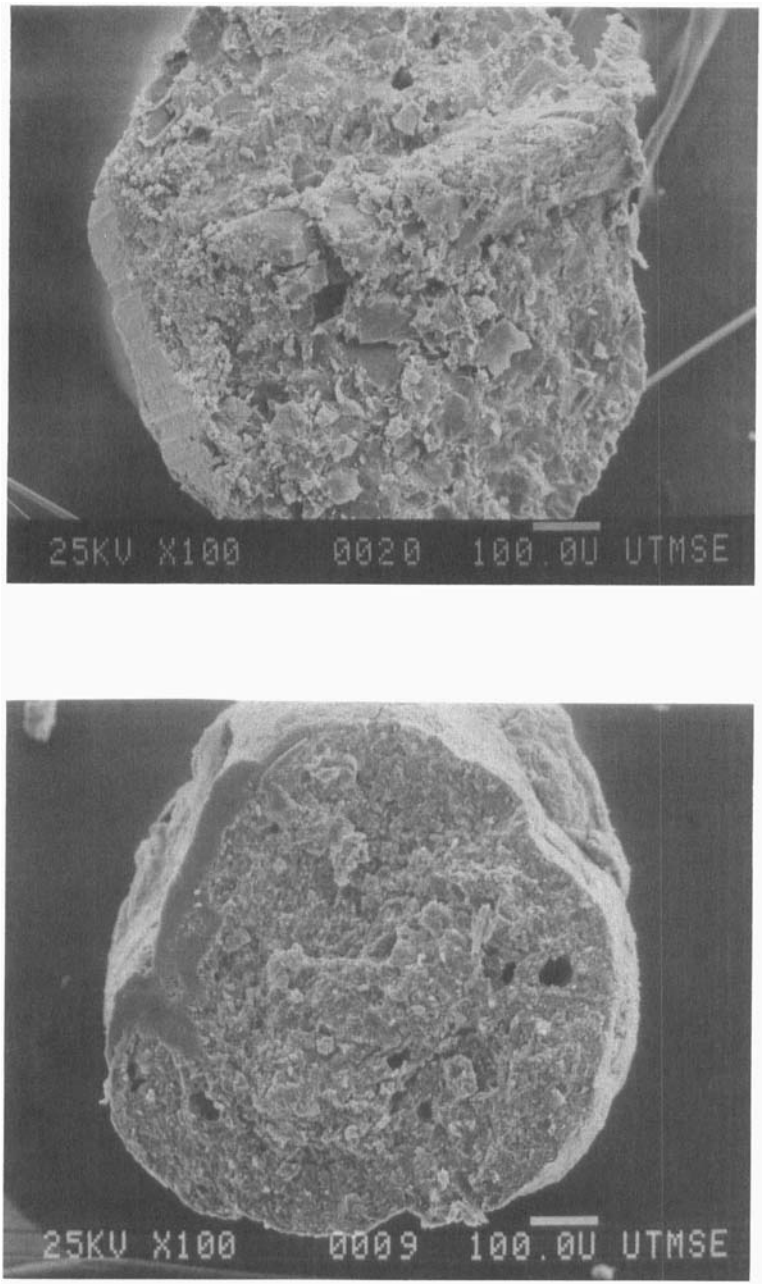

FIGURE 7

Scanning electron micrographs of the internal structure of beads. (a). The fracture surface of lactose-rich bead. (b). The transverse section surface of MCC-rich bead.

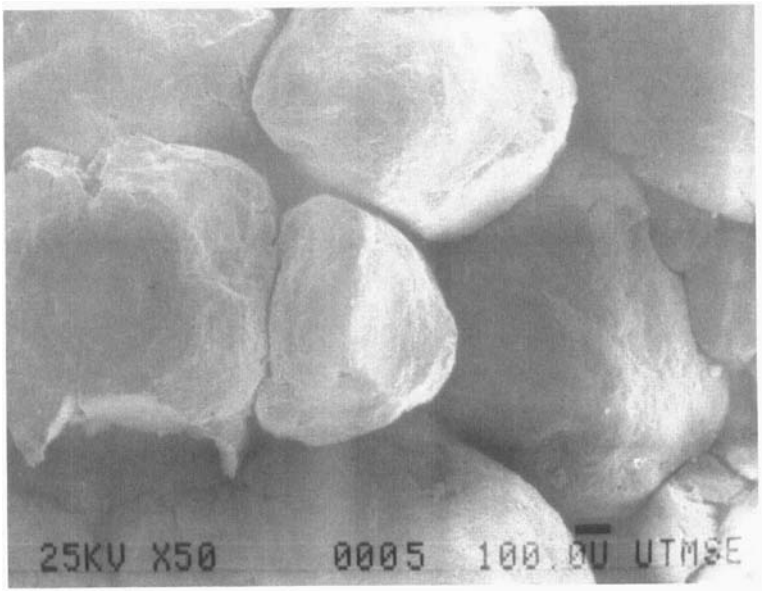

FIGURE 8

Scanning electron micrographs of the fracture surfaces of compacts made from different bead formulations. (a). MCC-rich bead. (b). Lactose-rich bead. (c). Lactose-rich bead/MCC-rich bead=1/1.

granule boundary may also confine the fibrous nature of MCC and limit the mechanical interlocking effect of the MCC-rich beads. Those bonding conditions were reflected in the differences in the values of bonding indices. It should be noted that the interparticular gaps were enlarged by the deforming and pulling effect of the stress applied to fracture the compacts in the tensile test, and the fracture surfaces do not represent the real bonding conditions.

In conclusion, while the MCC-rich beads showed poor compaction properties, the lactose-rich beads exhibited relatively good compactibility and higher bonding ability, properties which were reflected by the high tensile strength and bonding index. The poor compactibility and bonding ability of MCC-rich beads may be ascribed to the loss of its plastic nature during the granulation processes, the time-dependent viscoelastic expansion properties, and the confinement of fibrous nature

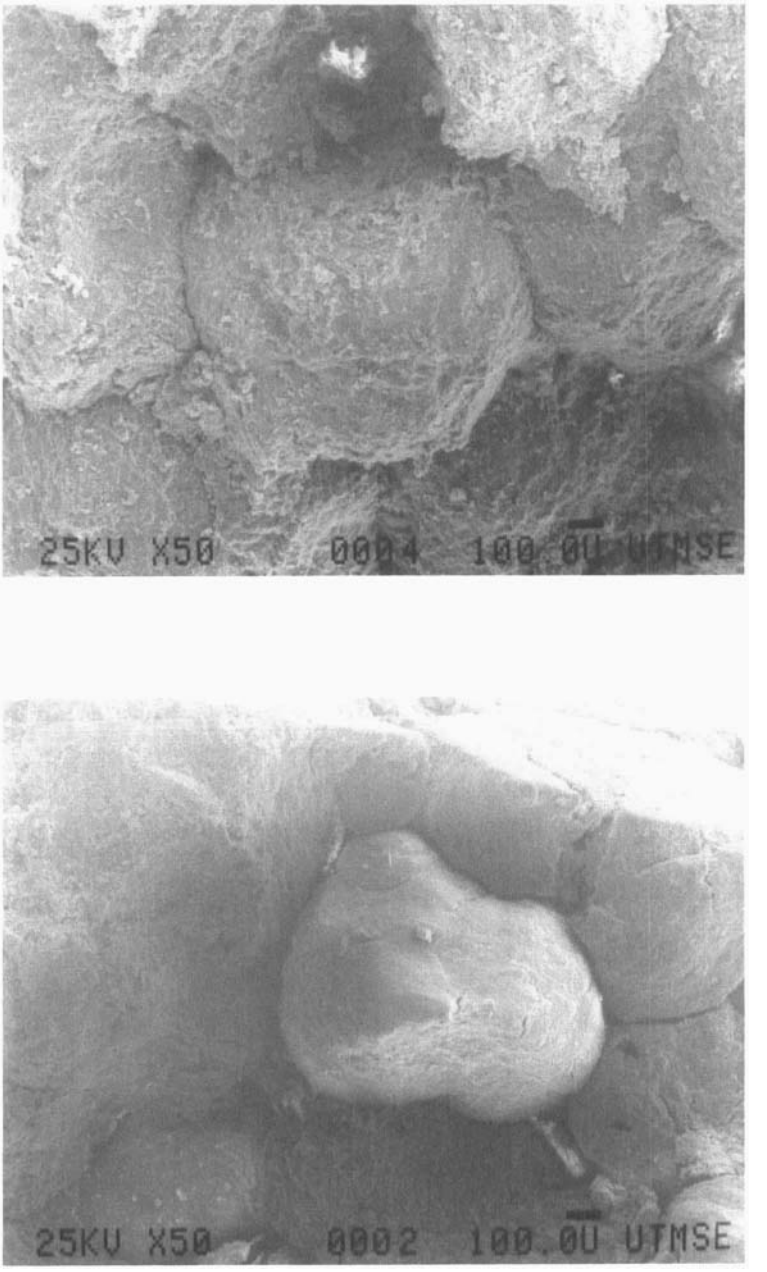

FIGURE 8. Continued

of MCC due to strong granule boundaries formed in the extrusion/spheronization process. The major factors which determined the physical-mechanical properties of the compacts composed of bead formulations were the properties of the beads themselves and interparticular mechanical interlocking. Interparticular forces at the molecular level were insignificant for the compaction of beads due to their large particle size. The results of this study demonstrated a ratio of lactose-rich beads to MCC-rich beads needs to be at least 2:1 in order to form compacts of acceptable mechanical strength.

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