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Research Article

Evaluation of the Performance Characteristics of Bilayer Tablets: Part I. Impact of Material Properties and Process Parameters on the Strength of Bilayer Tablets

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Abstract. Bilayer tableting technology has gained popularity in recent times, as bilayer tablets offer several advantages over conventional tablets. There is a dearth of knowledge on the impact of material properties and process conditions on the performance of bilayer tablets. This paper takes a statistical approach to develop a model that will determine the effect of the material properties and bilayer compression process parameters on the bonding strength and mode of breakage of bilayer tablets. Experiments were carried out at pilot scale to simulate the commercial manufacturing conditions. As part of this endeavor, a seven-factor half-fraction factorial (2^{7-1}) design was executed to study the effect of bilayer tablet compression process factors on the bonding strength of bilayer tablets. Factors studied in this work include: material properties (plastic and brittle), layer ratio, dwell time, layer sequence, first- and second-layer forces, and lubricant concentration. Bilayer tablets manufactured in this study were tested using the axial tester, as it considers both the interfacial and individual layer bonding strengths. Responses of the experiments were analyzed using PROC GLM of SAS (SAS Institute Inc, Cary, North Carolina). A model was fit using all the responses to determine the significant interactions ($p<0.05$). The results of this study indicated that nature of materials played a critical role on the strength of bilayer compacts and also on mode of fracture. Bilayer tablets made with brittle materials in both the layers are strongest, and fracture occurred in the first layer indicating that interface is stronger than layers. Significant interactions were observed between the selected factors and these results will provide an insight into the interplay of material properties, process parameters, and lubricant concentration on the bonding strength and mode of breakage of bilayer tablets.

KEY WORDS: axial tester; bilayer tablets; DOE; interfacial strength; process parameters.

INTRODUCTION

Bilayer tablets are generating great interest recently for the following reasons:

- Bilayer tablets provide a potential means of reducing the pill burden for patients as they can administer two or more active pharmaceutical ingredients (APIs) in a single FDC (fixed dose combination) dosage form (1).
- In some cases bilayer tablets are designed to overcome chemical incompatibility between two active components. In some chemically sensitive cases an inert layer is added between the two layers to prevent their contact (2).
- Bilayer tablets are also developed to achieve a desired drug release profile of the active component present in one layer by utilizing the functional property (hydrostatic and osmotic potential) of other layer. Bilayer tablets can be used to control the delivery rate of one or two different active pharmaceutical ingredients by sandwiching one or two inactive layers, in order to achieve swellable/erodible barriers for modified release (3).
- Bilayer tablets offer other advantages like: prolonging the patent life of a drug product (4), increased efficacy of the active components due to their additive or synergistic effect (5), reduced toxicity (6), improved adherence to treatment regimens by patients (7), convenience of use (1), and facilitating the logistics of procurement, distribution, and dispensing.

The above discussed advantages and capabilities are specific to bilayer tablets that are not achievable by single layer tablets, but bilayer tableting offers a new set of challenges for formulation design, manufacturing process, controls, and product performance requirements. A comprehensive understanding of both the product and process will address challenges in manufacturing, such as accuracy in weight control of

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individual layers (2), delamination/layer-separation during manufacturing, and storage (8), insufficient tablet breaking force (6), cross-contamination between the layers (especially for incompatible APIs) (9), and reduced yield (6).

Dietrich *et al.* (10) studied the influence of tableting forces and lubricant concentration on the adhesion strength of bi- and tri-layer tablets. They developed a statistical regression model based on the study conducted on a single station stationary press at laboratory scale and successfully validated the model on a rotary press at the commercial scale, but they have considered only two factors. Inman *et al.* (8) studied the effects of die wall forces, layer forces, and layer (radial) relaxation on the tensile strength and mode of fracture of bilayer micro crystalline cellulose tablets. Ozkan and Briscoe (11) relied on the surface topography of compacts as a means to optimize compaction conditions. They compacted spray dried alumina powder at various compaction pressures and cylinder aspect ratios. Radial and lateral surface topography characterization was performed to determine the nature and extent of the internal deformation of the agglomerates along the diameter and height of the cylindrical compacts. In addition, lateral surface topographical data has been used for the characterization of the die wall pressure distribution developed in the compressed cylindrical alumina compacts.

Most of the previous work has been done at the laboratory scale, on stationary single punch presses, in which the effect of only few variables on the adhesion strength of the bilayer tablets was evaluated. This paper takes a statistical approach to develop a model that will determine the effect of material properties and bilayer compression process parameters on the bonding strength and mode of breakage of bilayer tablets. Experiments were carried out at pilot scale on a rotary bilayer press to simulate the commercial manufacturing scenario, so that statistical trends obtained at this scale will be valid at the larger scale. This approach provides the rationale and guidance for the selection of materials and process parameters during the development of bilayer tablets. Part II of this paper will focus on a statistical approach to assess the impact of storage conditions on the bonding strength of bilayer compacts manufactured as part of this study.

FACTORS FOR DESIGN OF EXPERIMENTS (DOE)

Material properties and process parameters that play a key role in the performance of bilayer tablets are selected. Rationale for the selection of each factor is described below.

(a) *Materials*: Brittle and plastically deforming materials have a significant impact on the compaction process. A brittle (lactose) and a plastic material (Avicel) were evaluated in both the layers. Wu *et al.* (12) reported that compaction of the plastic material is by virtue of the plastic flow as long as the stress developed by the elastic recovery does not exceed the bond strength. On the application of compressive force, brittle material tends to fracture and fill the voids. Due to differences in their Young's modulus, brittle and plastic materials relax at different rates during decompression. Roberts and Rowe (13) reported the Young's modulus of Avicel and lactose is 13.2 and 53 GPa, respectively. Elastic mismatch of the adjacent layers in a bilayer tablet is due to differences in the Young's modulus and deformation histories of the individual layers. This will lead to generation of radial stresses which in turn will cause the bilayer tablets to delaminate. Propagation of force through the materials also changes with the material properties and forces applied. As a result of these aforementioned mechanisms, material properties and their sequence in bilayer tablets will strongly influence the strength (of the interface and individual layers) and mode of breakage. Four-layer sequences were studied as part of this DOE: Avicel/Avicel, lactose/lactose, Avicel/lactose, and lactose/Avicel.

(b) *First-Layer Force*: Studies carried out by Akseli *et al.* (14) have shown that first-layer force plays a significant role on the interfacial morphology, and hence on the interfacial strength of bilayer tablet. For plastically deforming materials in the first layer, increasing the first-layer force will reduce the surface asperities, which leads to the reduction of traction and a weak interface. Inman *et al.* (8) reported that a certain amount of interfacial roughness of the initial layer is required for particle interlocking and adhesion with the second layer. As the surface roughness of the first layer is reduced, the contact area for the second layer is significantly reduced at the interface, resulting in the weaker adhesion of the adjacent layers at the interface (8). If the first layer is not compressed before addition of the second layer, there is a possibility of uncontrolled mixing of first-layer material with the second-layer material at the interface (15). In addition, due to the centrifugal force during the rotation of the turret, first-layer material may shift toward the outer periphery of the die cavity resulting in an uneven (angled) interface. To produce visually appealing bilayer tablets, it is necessary to have a clear demarcation between the two layers. It will also prevent the chemical instability due to cross-contamination of the active components (15) (levels studied: low, 2 kN; center point, 3 kN; high, 4 kN)

(c) *Second-Layer Force*: Also known as main compression force, plays a significant role in the consolidation of tablets. For the same main compression force applied, materials with different properties deform and relax at different rates. Immediately after final compaction, the compressed second layer may release the stored elastic energy unevenly and may produce a crack at the interface of the adjacent layers which could act as a stress concentrator, eventually making the tablet interface weaker (16). This may result in capping or delamination of the tablet along the interface during manufacturing or immediately after manufacturing (8) (levels studied: low, 14 kN; center point, 18 kN; high, 22 kN).

(d) *Compaction Speed*: It has been widely referenced in the literature that dwell time plays a significant role in the compaction of bilayer tablets. Lower compaction speed increases the dwell time and results in a better consolidation compared to tablets made at a higher compaction speed (17). Apart from dwell time, compaction speed also plays a significant role in the flow of powder on the turret and into the die, which may result in layer weight variations for the two formulations. This becomes critical if there is a huge

difference in the layer weights (levels studied: low, 10 rpm; center point, 15 rpm; high, 20 rpm).

(e) *Layer Weight Ratio*: Weight of the two layers in a bilayer tablet are not always the same during the design of bilayer tablets. In most cases, there will be a huge difference in the ratio of their weights. In this extreme case, it is hard to predict the influence of a particular layer property on the whole compact where layer ratio and layer sequence become critical (levels studied: low, 1:3; center point, 1:1; high, 3:1).

(f) *Lubricant Level*: Magnesium stearate is used as a lubricant in this study. The blended lubricant in the bulk distributes throughout the mixture or coats the surface of the particles (18). This provides lubrication and reduces the friction generated when powder particles come in contact with each other or with dies and punches during compression. Dietrich *et al.* (10) have concluded that in order to achieve a greater interfacial interaction between the layers, low lubricant concentration is necessary for the first layer. Tye *et al.* (17) reported that the impact of lubricant level on tablet strength is more for plastic materials compared to brittle materials. (levels studied: low, 0.25% Mg. st.; center point, 0.5% Mg. st.; high: 0.75% Mg. st.)

STATISTICAL DESIGN OF EXPERIMENTS (DOE)

A seven-factor half-fraction factorial design (2^{7-1}) was executed to study the effect of bilayer tablet compression process factors, material properties, and lubricant concentration on the bonding strength of bilayer tablets. Factors include: material properties (plastic and brittle), different layer ratios, different dwell times, layer sequence, first- and second-layer forces, and lubricant concentration. Each factor in the factorial design is evaluated at two levels (high and low). This design was chosen because it allows evaluation of all main effects and two-way interactions with limited number of runs. In addition to the 64 fractional factorial points, there were two replicates run of the four-layer sequences (Avicel/Avicel, lactose/lactose, Avicel/lactose, and lactose/Avicel) by layer (first and second) combinations. At each of these four combinations, two replicates were performed at the center of the remaining five factors for a total of 72 (64+8) runs. The responses for the DOE include breaking force and the mode of breakage (*i.e.*, whether the fracture has occurred at the interface of two layers or in one of the layers).

MATERIALS AND METHODS

Two widely used pharmaceutical excipients were used: microcrystalline cellulose (Avicel PH-102; FMC Biopolymer, Newark, DE), Fast Flo lactose (Foremost Farms, Baraboo, WI), and magnesium stearate (Tyco Mallinckrodt, St. Louis, MO) was used as lubricant. SAS software version 8.2 (SAS Institue Inc, Cary, North Carolina) was used for the statistical analysis. The SAS procedure GLM was used to perform the analysis of variance (ANOVA).

BILAYER TABLETS PREPARATION AND TESTING

Blends for the bilayer compression are binary mixtures of an excipient and magnesium stearate. Excipients are mixed with 0.25%, 0.50%, and 0.75% *w*/*w* magnesium stearate in a 22-L bin blender for 60 revolutions (3 min at 20 rpm). Bilayer tablets made for this DOE study were manufactured using a 12 station Piccola bilayer press equipped with the Director data acquisition and analysis system (SMI Inc, Lebanon, NJ). Bilayer tablets are compressed with 3/8 in. round flat-faced punches. Total weight of each tablet is 500 mg with each individual layer being 250 mg. Breaking force (or axial strength) of the bilayer compacts was characterized by the axial tester (MARK-10 Corporation, Copiague, NY). Bilayer compacts were individually glued to two compact holders (Fig. 1) using a cyanoacrylate based glue (LOCTITE®, Henkel Corporation, Avon, OH) and left for an hour to ensure a good adhesion (14). Compact holders were connected to the arms of load cell; bottom arm of the load cell was stationary while the upper arm moved at a constant velocity of 10 mm/min. The displacement of the upper arm was continued until the fracture of the bilayer compact. Peak force was obtained from the force–displacement plot. Axial testing is the most efficient way of characterizing bilayer compacts as compared to diametrical compression and shear testing (14). Axial testing is not dependent on the precise identification of interface (which is necessary for shear testing), and considers both the interfacial and individual layer bonding strengths. Cracks propagate to the regions of weakest bonding within the bilayer compact upon axially loading the system.

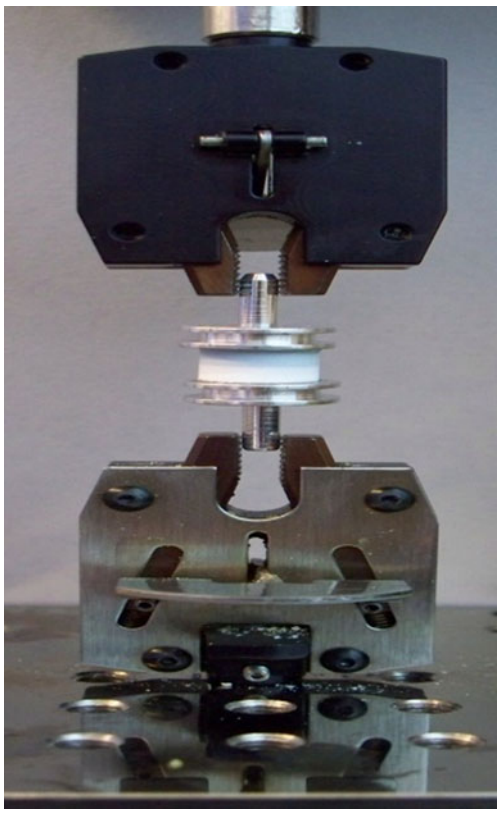

Fig. 1. A close-up photograph of the bilayer tablet to be tested

RESULTS AND DISCUSSION

Effects of the seven factors on breaking force were performed using PROC GLM of SAS (SAS Institute Inc, Cary, North Carolina). A model was fit using all 72 points that contained the seven main effects and 21 two-way interactions. The measured breaking force ranged from 0 to 159 N. The root mean square estimate (random error) from the full model is 16.38 N. An analysis of variance (ANOVA) model that included all main effects and two-way interactions was fit to the data. All of the terms in the model are listed in Table I. The model does not include terms that would allow estimation of separate curvature for each factor. No backward regression or other reduction in the full model was performed. The analysis is not trying to build a prediction model that would predict the response within the ranges of the factors but rather looking for whether or not there were differences between the low and high levels and if at these ranges, there were possible interactions between the factors.

Table I shows the *p* values associated with each term in the ANOVA model. Any term with a *p* value less than 0.05 was considered significant. This included layer 1 excipient, layer 2 excipient, compaction speed, and magnesium stearate level main effects, and the layer 1 by layer 2 excipient, layers 1 and 2 by compaction speed two-way interactions. No main effect plots are considered as they are all involved in two-way interaction. All significant two-way interaction plots are discussed below. Each significant two-way interaction and main effects that were not part of a two-way interaction are discussed in the following sections. This is a resolution V design which allows estimation of the main effects and two-way interactions cleanly. The seven-way interaction was used to create the 1/2 fraction. Therefore main effects are confounded with six-way interactions, two-way interactions are confounded with the five-way interactions and three-way would be confounded with the four-way interactions.

Table I. The *p* Values of the Different Interactions

Effect	*p* value
Layer 1 excipient (EX1)[a]	<0.0001
Layer 1 compression force (CF1)	0.0694
Layer 2 excipient (EX2)[a]	<0.0001
Layer 2 compression force (CF2)	0.4923
Excipient ratio (EXRatio)	0.4736
Compaction speed (CS)[a]	0.0024
Magnesium stearate level (MagSt)[a]	0.0045
EX1×CF1	0.2108
EX1×EX2[a]	<0.0001
EX1×CF2	0.0694
EX1×EXRatio	0.3172
EX1×CS[a]	0.0147
EX1×MagSt	0.7796
CF1×EX2	0.5114
CF1×CF2	0.4199
CF1×EXRatio	0.3318
CF1×CS	0.7450
CF1×MagSt	0.3623
EX2×CF2	0.3030
EX2×EXRatio	0.4829
EX2×CS[a]	0.0023
EX2×MagSt	0.1414
CF2×EXRatio	0.8146
CF2×CS	0.6340
CF2×MagSt	0.3946
EXRatio×CS	0.8500
EXRatio×MagSt	0.8857
CS×MagSt	0.0811

[a] Significant interaction

Effect of Materials on the Strength of Bilayer Compacts

Figure 2 shows the significant interaction found between the materials and material sequence on the strength of the bilayer tablets. Bilayer tablets made with brittle material (lactose) in both layers are stronger than the other three material combinations. These tablets fractured in the first layer upon loading axially, this indicates that the bonding strength between the two layers was higher than that of the individual layers. In brittle materials, the mechanism of consolidation is by fragmentation; so the elastic mismatch between the adjacent layers will be minimal if brittle materials are present in both the layers. Roberts and Rowe (13) reported the Young's modulus of Avicel and lactose as 13.2 and 53 GPa, respectively. Due to the rigid nature of the brittle materials (higher Young's modulus compared to the plastic materials) deformability capacity of the particles on the initial layer is significantly reduced, so there is substantial roughness still retained on the surface to provide nesting sites for mechanical interlocking (8).

Interfacial strength(s) of the compacts made with brittle (lactose) material in the first layer and a plastic (Avicel) material in the second layer are comparable with the *vice versa* layer sequence. These tablets fractured along the interface upon axial loading, indicating that the interface is weaker than each individual layer. Delamination of these tablets upon axial loading can be attributed to the elastic mismatch between the brittle and plastic layers (19). Elastic mismatch is generated due to the differences in deformation histories and Young's modulus values of the adjacent layers.

Interface was weakest for the compacts made with plastic (Avicel) materials in both layers, these tablets delaminated coming off the tablet press. Avicel is known to consolidate by plastic deformation and this will result in different deformation histories of both the layers and hence a substantial elastic mismatch between the layers to delaminate (19). The surface roughness of Avicel in the first layer was reduced

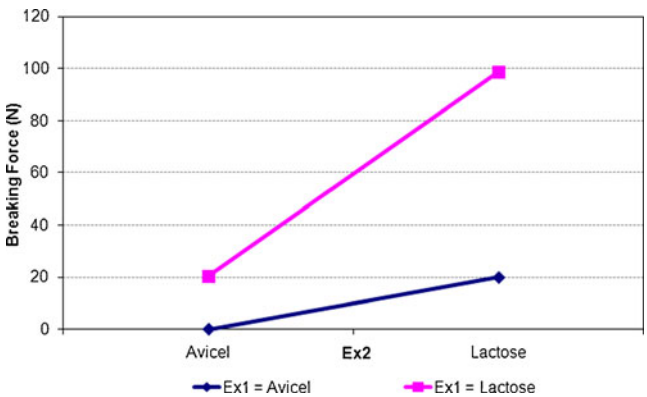

Fig. 2. Effect of materials on the strength of bilayer tablets (*Ex1* = material in layer 1; *Ex2* = material in layer 2)

significantly (at the first-layer forces: 2, 3, and 4 kN) thus resulting in a decrease in inter-particulate attraction and mechanical interlocking between the two adjacent layers.

Effect of First-Layer Material and Compaction Speed

Figure 3 shows the significant interaction found between the first-layer material and compaction speed on the strength of the bilayer tablet. For all the tablets, fracture occurred at the interface, indicating that the strength of individual layers is higher than the bonding strength between the two layers. Presence of the brittle material in the first layer increased the interfacial strength of the tablets compared to having a plastic material (Avicel) in the first layer. This effect can be attributed to the differences in their consolidation mechanisms. For ductile materials like Avicel, surface asperities decrease with the application of first-layer force, thus the possibility of mechanical interlocking reduces significantly. As brittle material is more rigid compared to plastic material it is less deformable, hence it retains more surface roughness for mechanical interlocking of adjacent layers.

For both materials in the first layer, tablets produced at lower compaction speed (longer dwell time) are stronger than those produced at higher compaction speed (shorter dwell time). Higher dwell time resulted in the formation of stronger compacts, presumably from better consolidation of particles (17).

Effect of Second-Layer Material and Compaction Speed

Figure 4 indicates that the interfacial strength was higher for the bilayer tablets made with brittle (lactose) material in the second layer than those tablets that were made with plastic material. Due to their differences in deformation mechanisms, compressed plastic material will store more elastic energy compared to a brittle material (8). As a result, tablets made with plastic material in the second layer relax unevenly and at a faster rate compared to the brittle material (due to the differences in the Young's modulus), thus producing the micro cracks at the interface which act as stress concentrators and weaken the tablet interface.

With the brittle material in the second layer, tablets produced at lower compaction speed (longer dwell time) are stronger than those produced at higher compaction speed (shorter dwell time). Lower compaction speed increases the dwell time and results in better consolidation compared to the tablets made at a higher compaction speed. Compaction speed has no effect on the strength of the bilayer tablet, if the second-layer material was plastic (Avicel). Breakage of all the tablets occurred at the interface.

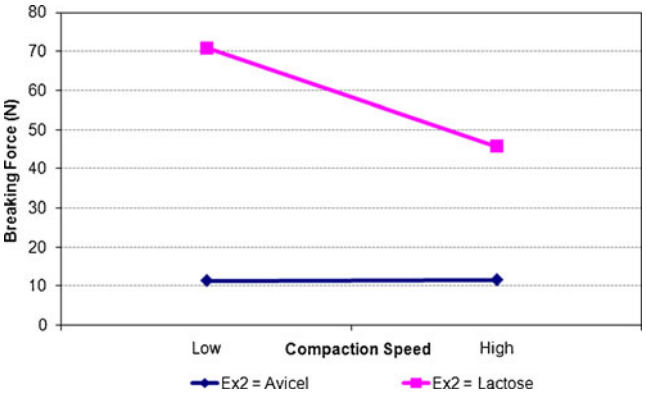

Fig. 4. Effect of second-layer material and compaction speed on the strength of bilayer tablets (*Ex2*=material in layer 2)

Effect of First-Layer Material and Second-Layer Compaction Force

As indicated in Fig. 5, the strength of the interface increased with an increase in second-layer force, when plastic material was in the first layer. Strength of the interface decreased with the increase of second-layer force, when the brittle material was in the first layer. This effect can be attributed to the plasticity of the first layer. With the plastic material in the first layer, increasing second-layer force will deform the first-layer material as it still retains some plasticity after the first-layer compaction (14). Retained plasticity of the first layer will allow the second layer to penetrate into the first layer increasing the bonding strength of the adjacent layers due to mechanical interlocking (14).

The deformability capacity of the first layer will decrease significantly with the presence of brittle material in the first layer. Deformation of the first layer will be minimal with an increase of the second-layer force due to the rigid nature of brittle material; as a result, there will be minimal penetration of second layer into the first layer (14). This will reduce the

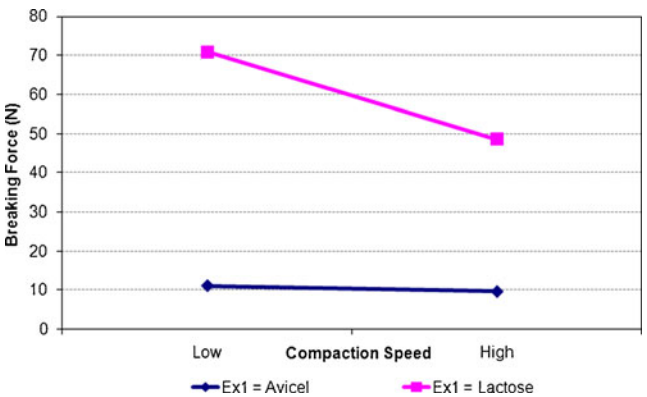

Fig. 3. Effect of first-layer material and compaction speed on the strength of bilayer tablets (*Ex1*=material in layer 1)

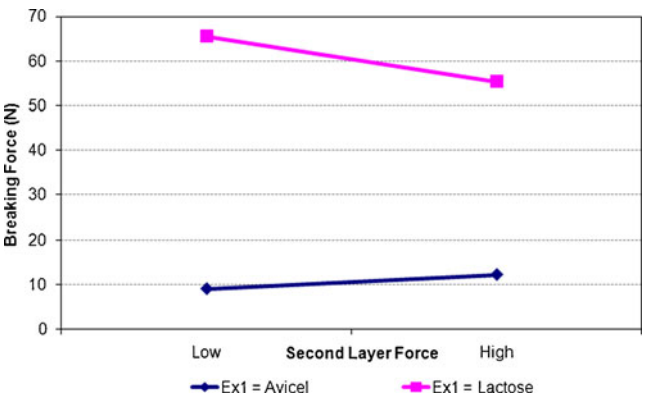

Fig. 5. Effect of first-layer material and second-layer force on the strength of bilayer tablets (*Ex1*=material in layer 1)

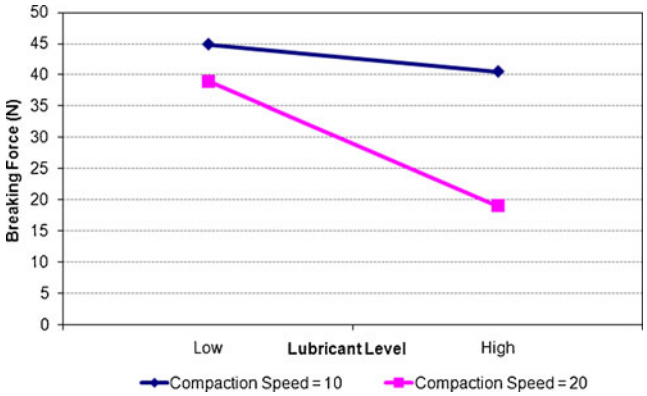

Fig. 6. Effect of compaction speed and lubricant level on the strength of bilayer tablets

mechanical interlocking of the adjacent layers and hence their bonding strength.

Effect of Compaction Speed and Lubricant Concentration

As shown in Fig. 6, interfacial strength decreased with the increase of lubricant concentration for both compaction speeds. The interaction plot of compaction speed and lubricant level shows that interfacial strength decreased slightly with an increase in compaction speed at low lubricant level. At high lubricant level, interfacial strength decreased with high compaction speed.

Increased lubricity of the powder blend will reduce the friction between the powder particles that contact with each other during compression, as the lubricant will distribute throughout the mixture and coat the surface of the particles (18). This mechanism will reduce the compact strength. A combination of higher lubricity and poor consolidation of the powder particles due to higher compaction speed (lower dwell time) will further reduce the tablet strength (10).

CONCLUSIONS

As expected, nature of materials played a critical role on the strength of bilayer compacts and also on mode of fracture. Bilayer tablets made with brittle materials in both the layers are strongest, and fracture occurred in the first layer indicating that interface is stronger than layers. Interface was weakest for the plastic tablets as they delaminated coming off the press. Delamination of the adjacent layers can be attributed to their elastic mismatch which was generated due to their different deformation histories. Differences in the consolidation mechanisms of the materials will also play a crucial role in determining the surface topography of the first layer, which provides nesting sites for mechanical interlocking of the layers.

A significant interaction was also found between the first-layer material and the compaction speed; interfacial strength was strongest for the compacts with brittle material in the first layer. For both the materials interfacial strength decreased with the increase of compaction speed. As lower compaction speed increases the dwell time and results in the better consolidation compared to the tablets made at higher compaction. Second-layer material has also showed a significant interaction with compaction speed on the strength of bilayer tablet; interfacial strength was strongest for the compacts with brittle material in the second layer.

A significant interaction was observed for the first-layer material and second-layer compaction force, for the plastic material in the first-layer strength of the interface increased with increase of second-layer force. For the brittle materials, strength of interface decreased by increasing the second-layer force. This effect is due to the retained plasticity of the first layer which allows the second layer to penetrate into the first layer increasing the bonding strength of the adjacent layers due to the mechanical interlocking.

A significant interaction was observed for the compaction speed and lubricant concentration. At high lubricant level, interfacial strength decreased with the increase of compaction speed. A combination of higher lubricity and poor consolidation of the powder particles due to higher compaction speed (lower dwell time) will further reduce the interfacial strength of the bilayer tablets.

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