CHARACTERIZATION OF PHARMACEUTICAL BILAYER TABLETS: A FRACTURE MECHANICS APPROACH

by

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ABSTRACT OF THE DISSERTATION

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Bilayer tablets are generating great interest recently in the pharmaceutical industry as they offer several advantages over conventional single layer tablets. However, the production of bilayer tablets has been facing great difficulties as the layered tablets are prone to delaminate at the interface and fracture in the individual layers due to insufficient bonding strength. Poor product performance is a cause of great concern as it will incur financial loses and regulatory liabilities. In the pharmaceutical industry the process of bilayer design has been heavily dependent on the trial-and-error approach during the formulation and process development stages. To overcome this hurdle it is critical to understand the mechanical properties of the materials and to develop a methodology for the characterization of bilayer tablets.

The work presented in this dissertation will focus on gaining the mechanistic understanding on the factors that impact the performance of the bilayer tablets. A methodology has been developed based on the principles of fracture mechanics for the characterization of bilayer tablets. As part of this endeavor, interfacial stress intensity was estimated. To understand the impact of manufacturing process parameters and

environmental conditions on the bonding strength of bilayer tablets a comprehensive DOE has been executed to obtain statistical trends.

Results indicated that material properties, compaction forces of the layers and interfacial topography have a strong influence on the strength of bilayer tablets. Strength of bilayer tablets increased with the increase of interfacial roughness and curvature. Physico-mechanical properties of the powders, deformation histories of the layers, and compression process parameters greatly influenced the interfacial stress intensity factor of the bilayer tablets. For the bilayer tablets made with plastic material in the first layer, the stress intensity factor is more dependent on interfacial radius of curvature than on interfacial roughness and *vice versa* in the case of bilayer tablets made with brittle material in the first layer.

The mechanistic understanding and the methodology developed for the characterization of the bilayer tablets in this dissertation will enable to move away from the existing "trial-and-error" approach during the design and development of bilayer tablets. The new paradigm of bilayer tablet development will incorporate the principles of the quality by design by leveraging the prior knowledge.

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Dedication

To **Lord Venkateswara**: For his kind blessings.

To every peasant on this planet.

To Smt. Raghavamma Paturi, and to all my teachers: For bestowing me the education.

And

To my Grandparents and Parents: For their boundless love.

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Chapter 1: Introduction

1.1 Motivation

Bilayer tablet is a fixed dose combination (FDC) that combines two or more active pharmaceutical ingredients in a single dosage form. Bilayer tablets are becoming increasingly popular, particularly as pharmaceutical manufacturers are seeking to reformulate their currently marketed products to extend their patent life or to improve their safety and therapeutic profiles. A wide range of fixed dose combination products are currently marketed in various therapeutic areas like virology, immunology, metabolic, and cardio-vascular. Table 1 provides the list of some fixed dose combination products available in the market. Bilayer tablets offer the following advantages over the conventional tablets:

- 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 swellables/erodible barriers for modified release [3].

- Bilayer tablets facilitate the treatment of different ailments in the same patient (co-morbidity), at the same time and with one dosage form.

- 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 individual layers [2], de-lamination/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].

Among the aforementioned challenges, a notable one during the design of the bilayer tablets is their tendency to delaminate at the interface or fracture within the bulk of the separate material layers during the various stages of bilayer tablet production or during

the downstream operations like tablet coating and packaging. In the pharmaceutical industry the process of bilayer design is heavily dependent on the trial-and-error approach during the formulation, process development, and at scale-up stages. Understanding and predicting the mechanical strength of the bilayer tablets is of commercial significance since poor performance of these tablets due to weak mechanical strength can lead to enormous financial loses and regulatory liabilities [10]. To overcome this hurdle it is critical to understand the mechanical properties of the materials and to develop a methodology for the characterization of bilayer tablets.

The work presented in this dissertation will focus on understanding the influence of bilayer compression process parameters, physico-mechanical properties of the materials, and interfacial topography on the fracture patterns and strength of the bilayer tablets. Novel characterization tools were explored to evaluate the interfacial roughness and strength of bilayer tablets. A methodology has been developed for the characterization of bilayer tablets based on the principles of fracture mechanics. Characterization of the bilayer tablets was carried out through the estimation of the stress intensity factor. Impact of bilayer compression process parameters, materials and interfacial properties on the interfacial critical stress intensity factor (K_I) was established.

As part of this work, a statistical model has been developed to determine the effects of material properties and bilayer compression process parameters on the bonding strength and the mode of breakage of the bilayer tablets. As part of this endeavor, a seven factor half-fraction factorial (2^{7-1}) design was executed. Factors studied in the statistical design

are: material properties (plastic and brittle), layer ratio, dwell time, layer sequence, first and second layer forces, and lubricant concentration. Experiments were carried out at a 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. Statistical trends obtained from this approach will provide the rationale and guidance for the selection of the materials and process parameters during the development of the bilayer tablets.

Bilayer tablets will be exposed to different ambient conditions after their manufacture during downstream operations like tablet coating, packaging, and shipping. Humidity and temperature along with the storage time are reported to play a crucial role in determining the mechanical characteristics of the bilayer tablets. As with conventional single layer tablets, physical stability of bilayer tablets during storage is a key factor for consideration during product development as this may impact the tensile strength, friability, disintegration, dissolution and other performance characteristics of the bilayer tablets. Affinity for the water adsorption changes with the materials and this difference in the material-water interaction might lead to the differences in the radial and axial expansions in the layers of the bilayer tablets which result in radial stresses at the interface. The work presented in this dissertation will also evaluate the impact of environmental conditions on the performance of the bilayer tablets.

The four specific aims of this dissertation are as follows:

Specific Aim 1: Understand the influence of compaction properties and interfacial topography on the performance of bilayer tablets (Chapter 2).

Specific Aim 2: Develop a fracture mechanics model for the characterization of bilayer tablets and to evaluate the impact of bilayer compression process parameters, materials and interfacial properties on the interfacial stress intensity factor (K_I) (Chapter 3).

Specific Aim 3: To evaluate the impact of bilayer compression process parameters and material properties on the strength of bilayer tablets (Chapter 4).

Specific Aim 4: To evaluate the impact of environmental conditions on the strength of bilayer tablets manufactured with different materials and compression process parameters (Chapter 5).

1.2 Characterization of Bilayer Tablets

1.2.1 Mechanical Strength

Figure 1-1 depicts the steps involved in the manufacturing of the bilayer tablets. The process involves filling the die with the bottom layer material and tamping with a lower force to remove the entrapped air and form a loose compact. Next step involves filling the die with the second layer material and applying the main compression force, this will be followed by the ejection of the compact from the die.

As with the monolayer tablets, determination of the mechanical strength of the bilayer tablets (manufactured by the above procedure) is critical for the following reasons:

- Mechanical strength is a key quality attribute that needs to be monitored and controlled during the production of bilayer tablets. It ensure that tablets are strong enough to withstand the stresses generated during the handling and downstream operations like tablet coating and packaging.

- It is critical in obtaining a fundamental understanding of compaction mechanisms.
- It also assists in the characterization of the mechanical properties of the compacted material.

In the literature several tests have been reported for assessing the mechanical strength of the tablets. Flexure test or bending test is one such test, in this test the specimen in the form of a parallel beam is subjected to three or four point bending and the maximum tensile stress estimated from the load at fracture (Figure 1-2). The essential feature of flexure test is that under the correct conditions of loading, the specimen will be subjected to a pure longitudinal tensile stress along a line on the opposite surface to that on which the load is applied. Berenbaum and Brodie [11] used the four-point loading to estimate the tensile strength of rectangular beams and found that the stress distribution in the specimen is non-uniform, varying from zero at the neutral axis to a maximum at the outer edge surface. Mashadi and Newton [12] have prepared the beams of rectangular cross section from pharmaceutical materials and tested them using the three-point loading method to characterize the material properties of compacted powders. Rectangular beams are not a conventional tablet shape and the density distributions developed during beam formation are unlikely to be the same as those produced in a right circular cylinder. David and Augsburger [13] used the three-point flexure test to measure the tensile strength of the round flat faced tablets. One problem with such approach is that the dimensions of the tablets are unsuitable, to allow a valid application of the equations derived from the theories of bending. A bending moment will be produced by virtue of the test design, which will drastically reduce the strength of the compact. There is also a likelihood of the large contribution of the shear stresses at failure. Flexure testing is not an appropriate

technique to characterize the circular compacts or thin square compacts where the shear stresses significantly affected the results obtained.

Diametrical compression is the most commonly used test for measuring the mechanical strength of the tablets in the pharmaceutical industry. It overcomes the above discussed disadvantages of the flexure testing. In diametrical testing, cylindrical tablets are subjected are subjected to two diametrically opposed point loads. Specimens will fail at the loading points due to the compressive stresses and not in the central part of the specimen due to the tensile stress. Rudnick et al. [14] reported that fracture of does not always extend right to the ends of the diameter. A second fracture pattern, the triple-cleft failure has also been identified as being failure in tension. They concluded that compressive occurs at the specimen surface immediately beneath the loads where the compressive stresses are at a maximum and appears as local crushing. If this crushing is not extensive it may only result in an increase in the area over which the load is applied so that ultimate failure may be in shear or tension. Photoelastic studies conducted by Hartog [15] revealed that material properties of the platen will modify the stress distribution within the disc. Platens made of different materials such as steel, rubber and card board produced different stress patterns. Experimentally determined fracture strengths indicated that the lower the elastic moduli of the platens the higher was the apparent tensile strength and greater the variance of the results.

Above discussed flexure testing techniques employ complex experimental setups and require direct comparison of the mechanical properties values calculated from different analytical solutions. Due to the complexity involved in the testing techniques they are not

used in the regular manufacturing setting for measuring the mechanical strength of the bilayer tablets. Unlike monolayer tablets (homogenous), bilayer tablets are heterogeneous structures containing an interface. In addition to the strength of the individual components interfacial strength is critical and plays a vital role in the performance of the bilayer tablets. Due to the presence of multiple components determination of the mechanical strength of the bilayer tablets is challenging and the measurement techniques used for characterizing the monolayer tablets will not provide the relevant data. Axial testing is the most preferable way to characterize the bilayer tablets as it allows loading the interface and allows the bilayer tablets to fracture at the regions with the weakest structural strength. Brittleness is the key property of pharmaceutical powders. Cracks in brittle tablets are most likely to propagate under the influence of tensile stresses, and brittle cracks will always seek an orientation that minimizes the shear loading. Axial loading is therefore essential for the characterization of brittle tablets. Axial testing will also overcome the problem of interface identification (as the pharmaceutical bilayer tablets have the curved interfaces due to the cup depths of punches) associated with the shear loading.

1.2.2 Characterization of Bilayer Interface

Studies conducted by several researchers have indicated that topography of the bilayer interface will play a salient role in the performance of the bilayer tablets. Material properties along with compression process parameters will control the surface properties of the bilayer interfaces. Hence, it is critical to employ the right tools and methodology for the characterization of bilayer interfaces.

Experimental methodologies to determine interfacial topography include optical microscopy, scanning electrical microscopy (SEM), laser profilometry, and stylus based perthometer. Karehill et al. [16] performed SEM studies to determine the surface characteristics of bilayer tablets made with various pharmaceutical materials. They reported that for plastically deforming materials such as microcrystalline cellulose and sodium chloride bonding strengths between adjacent layers decreased with the decrease of interfacial surface roughness. The bonding strengths between layers of fragmenting materials such as lactose and calcium phosphate were insensitive to roughness since the area of contact was maximized between fragmented particles after their initial fracture. Podczeck et al. [17] used optical profiling to determine topographic changes of tablet surfaces with coating time, however, no significant correlation could be made. Narayan and Hancock [18] correlated the determined roughness parameters of tablets of several pharmaceutical excipients with their mechanical strength properties. A clear distinction was found between the brittle tablets: displaying low values of R_a and R_s with high variability and negative skewness, and plastic materials which deform in a ductile manner: displaying higher values of R_a and R_s. Narayan and Hancock [18] extended on this study by investigating the effect of particle size on the obtained roughness parameters for tablets with a predilection to deform in either a predominantly plastic or brittle manner. They concluded that the relationship was complex in nature and the roughness was influenced by several factors including the yield stress, ductile/brittle transition particle diameter, the compaction stress and the mean particle diameter, hence further studies were required to obtain conclusive correlations. Bashaiwoldu et al. [19]

correlated their obtained roughness parameters with the porosity of pellets prepared under varying conditions, and concluded that structural changes, including variations in porosity due to elastic relaxation, of the pellets could be determined from topographic measurements. As part of this research work, stylus profilometry was employed for the characterization of the interfacial topography.

Background sections of the chapters 2, 3, 4, and 5 will discuss the literature specific to the chapter.

1.3 Figures for Chapter 1

Figure 1-1: Different steps involved during the manufacturing of bilayer tablets
[Source: O. Koo, 2010]
(a) First layer fill; (b) First-layer tamping; (c) Upper punch withdrawal; (d) Second layer fill; (e) Main compression; (f) Ejection

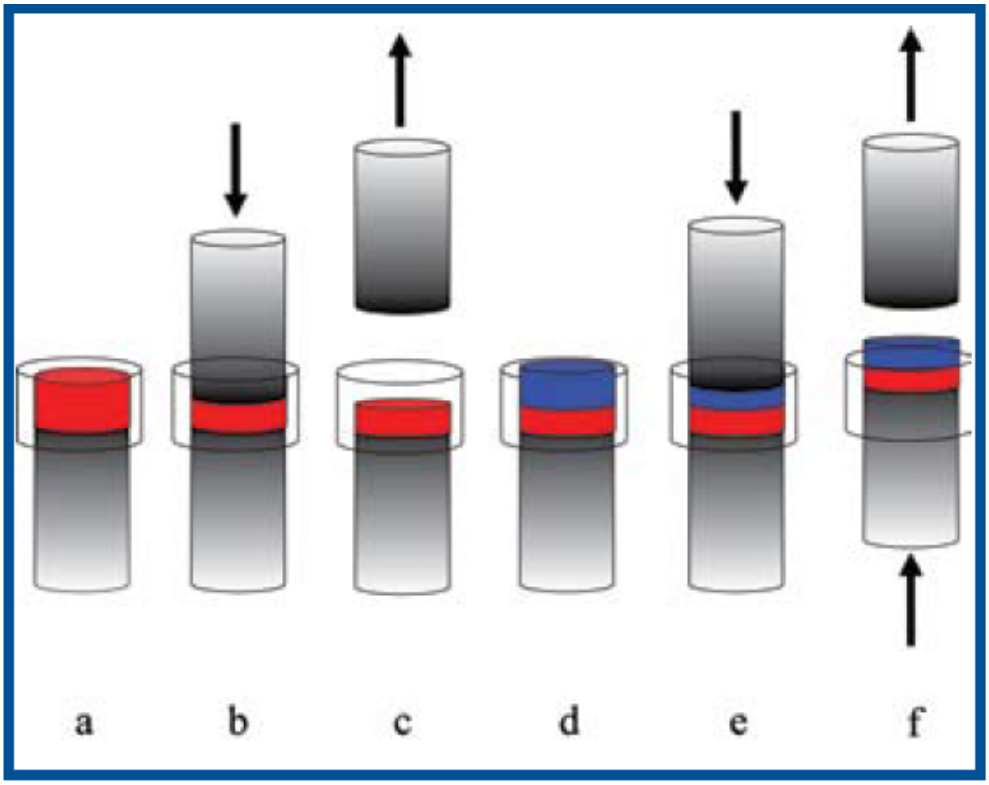
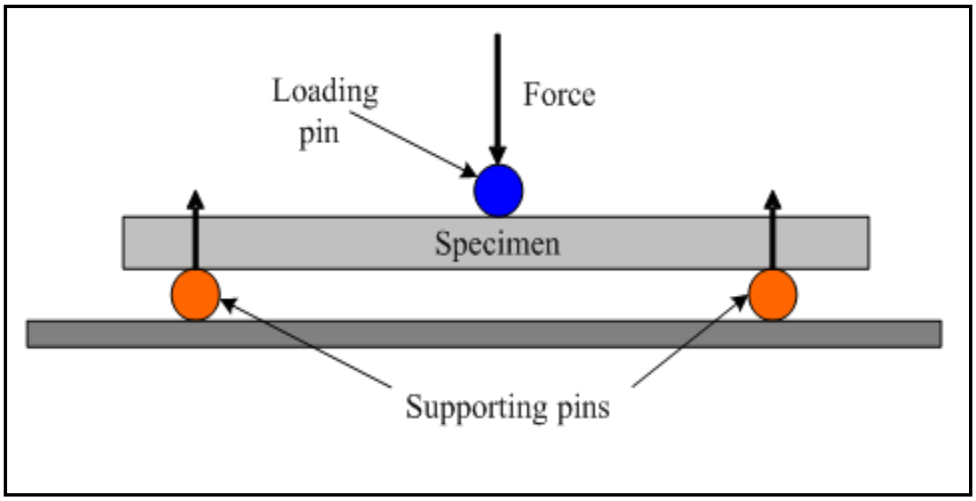


Figure 1-2: Schematic of flexure testing (3 point bending)
[Source: http://www.substech.com/dokuwiki/doku.php?id=flexural_strength_tests_of_ceramics**]**



1.4 Tables for Chapter 1

Table 1-1: List of fixed dose combinations (FDCs) currently marketed in various therapeutic areas

Virology	Cardiovascular	Metabolic	Other
• Combivir (zidovudine+ lamivudine) • Epzicom: (abacavir + lamivudine) • Trizivir: (zidovudine/abacavir + lamivudine) • Atripla: (emtricitabine/tenofovir + efavirenz)	• BiDil: (isosorbide dinitrate + hydralazine HCl) • Vytorin: (ezetimibe + simvastatin) • Caduet: (amlodipine + atorvastatin)	• Janumet: (Sitagliptin+ Metformin) • Kombiglyze (Saxagliptin+Metformin) • Glucovance (Glyburide+Metformin)	• Zyrtec – D: (cetirizine +Pseudoephedrine) • Treximet (sumatriptan + naproxen sodium)

Chapter 2: Influence of compaction properties and interfacial topography on the performance of bilayer tablets

2.1 Background

Delamination (separation of individual layers at interface) and/or fracture within the bulk of the separate material layers is a cause of great concern during the design and production of bilayer tablets in the pharmaceutical industry. The stress distribution caused during the loading of the particles and the resultant inhomogeneity of the localized regions of the stored elastic energy is the cause of the tablet fracture [8]. According to the principles of fracture mechanics, the fracture of bulk material and the delamination of material layers are two aspects of the same phenomenon i.e. the failure of a solid body due to an excessive loading condition [20]. Tablets are inhomogeneous porous bodies incorporating many cracks and flaws inside the bulk and along the interface of the adjacent layers. The cracks and flaws introduce stress singularities into the tablets, and the maximum stress acts at the tip of them. In a bilayer tablet, bulk layers fail due to crack propagation into one of the individual layers, and bilayer tablets delaminate due to crack propagation along the interface. This process consumes energy, and it is thus important to understand where during the manufacture of bilayer tablets this energy is generated and how much is required to cause the tablets to fail [20].

Understanding and predicting the mechanical strength of these tablets is of commercial significance since the bilayer tablet failures due to weak mechanical strength can lead to enormous financial loses [10]. The formulations used for each individual layer should be compressible and compactable on their own i.e. they should show satisfactory reduction in volume and form mechanically strong, coherent solid bodies. Under this assumption

the interface between the layers should bond together during compaction and strong adhesion forces should hold the layers together after ejection. However, this is not always the case, and as compressibility and compactibility of the individual layers may not be the cause for delamination, other physical mechanisms need to be identified that can explain the problems with delamination [20]. Karehill et al. [16] reported that the compaction pressure used to form the first compact layer should be kept at a minimum to provide sufficient surface roughness for nesting and particle interlocking between layers to occur. Due to increase in surface roughness there is a larger contact area between the layers, which enhances interlayer adhesion. Anuar and Briscoe [21] reported that the delamination of bilayer tablets is due to the development of various mechanical stresses during compaction and particularly during the unloading phase and tablet ejection. Podczeck and Al-Multi [22] reported that if the material forming the lower layer of a bilayer tablet was more elastic then the tension introduced into the system weakened the strength of the bilayer tablets. Dietrich et al. [23] used a shear apparatus to measure the shear forces needed to separate the layers in the radial direction and these shear forces were regarded as a measure of adhesion strength. Podczeck et al. [24] measured the tensile strength of bilayer tablets, which are rectangular beams consisting of two layers of equal thickness, using three-point bending tests and found that the value of tensile strength was either greater or lower than the tensile strength of the beams of the same thickness composed of the same materials, which cannot even be corrected by considering the differences in the elasticity of the materials in layered tablets. They anticipated that the way in which the failure of the beam crossed the interface between different layers was an important factor in determining the tensile strength of bilayer

tablets using this test. However, despite all these reports, the reasons for delamination of bilayer tablets were not completely identified and it is also necessary to formulate an experimental methodology to characterize and predict the performance of the bilayer tablets.

Following are the objectives of this work: i) understand the effect of material properties, and layer forces on the mode of crack propagation and tensile strength of tablets; ii) to investigate the influences of interfacial topography and mechanical properties on the fracture patterns of the bilayer tablets loaded axially; iii) to assess the influence of deformation history of materials and surface topography of the first layer on the tensile strength of tablets; iv) to examine the effect of layer sequence and layer forces on the interfacial curvature and the tensile strength of tablets; v) to determine the impact of lubricant concentration on the strength of bilayer tablets.

In this study we used tools which are different from the ones used to characterize the conventional single layer tablets. To evaluate the tensile strength of bilayer tablets we have employed axial tester instead of diametrical compression test [25]. For bilayer tablets, diametrical compression test is not an appropriate characterization tool to evaluate the adhesive strength of the interface due to their heterogeneous structure, which may result in different stress distributions from those developed in conventional single layer tablets.

2.2 Materials and Methods

2.2.1 Materials

Two widely used pharmaceutical excipients were used: Microcrystalline cellulose (Avicel PH-102; FMC Biopolymer, Newark, DE) and Fast Flo lactose (Foremost Farms, Baraboo, WI) were used as representative dry binder/diluent excipients. The mean particle sizes of the MCC and Fast Flo lactose are 100 μm and 75 μm, respectively. Magnesium sterate (Tyco Mallinckrodt, St. Louis, MO) was used as lubricant.

2.2.2 Bilayer Tablet Preparation

Blends for the bilayer compression are binary mixtures of an excipient and a lubricant. Excipients are mixed with 0.25 and 0.75% w/w of their weight with magnesium sterate in a 22L bin blender for 60 revolutions (3 minutes at 20 rpm). Bilayer tablets made for this study were manufactured by uni-axial compression using an Instron Universal Testing System (Model # 5567, Instron Corporation, Norwood, MA). In this machine the bottom punch is stationary while the top punch is moving at constant velocity of 10 mm/min. A round flat-faced punch with a diameter of 3/8" is used. Bilayer tablets were manufactured by manually filling the die with the first layer material followed by the application of the first layer force using upper punch. A semi-circular shaped aluminum foil of 3/8" diameter and 0.03 mm thickness was placed on the surface of the compacted first layer. Then the second layer material was manually filled into the die followed by the application of second layer force. The semi-circular shaped aluminum foil at the interface of the adjacent layers will cover half the surface of the interface and will act as a crack. This configuration will allow us to study the crack propagation mechanisms and also to

estimate the stress intensity factor (K_I) of the interface using the properties of the crack. Estimation of stress intensity factor is beyond the scope of this chapter and will be discussed in chapter 3.

2.2.3 Bilayer Tablet Testing

At each set of parameters bilayer tablets were made in triplicates and their breaking force was determined. Breaking force (or axial strength) of the bilayer tablets was characterized by the axial tester (MARK-10 Corporation, Copiague, NY). Bilayer tablets were individually glued to two tablet holders using a cyanoacrylate based glue (LOCTITE®, Henkel Corporation, Avon, OH) and left for an hour to ensure a good adhesion [25]. Tablet 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 catastrophical fracture of the bilayer tablet. Peak force was obtained from the force-displacement plots. Axial testing is the most efficient way of characterizing bilayer tablets as compared to diametrical compression and shear testing. 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. Crack will propagate to the regions of weakest bonding with-in the bilayer tablet upon axially loading the system.

2.2.4 Surface Roughness

We have used stylus profilometry technique to evaluate the roughness of the surfaces. Stylus instrument enables two-dimensional tracing of a surface. The stylus is traversed

normal to the surface at constant speed. Traced profile is the enveloping profile of the real surface acquired by means of a stylus instrument. The traced profile consists of form deviations, waviness and roughness components. Perthometer (Mahr Federal Inc. Providence, RI) is used as a characterization tool to generate roughness profiles of interfaces of bilayer tablets. For a tablet of 3/8'' diameter around 19,000 data points are collected. Average of these values gives the average roughness (R_a) and standard deviation value of these data points is the Root Mean Square (RMS) roughness of the surface. RMS roughness values indicate the tortuosity of the interface.

Roughness is usually measured as a summation of negative and positive deviations from a 'mean plane' fit over the surface of interest. Figure 2-1 shows an example of a roughness profile where variations in the *z*-direction are depicted as a function of *x*. Typical roughness parameters defined below in the following relations:

Average roughness R_a is the arithmetic average of the absolute values of the roughness profile ordinates.

$$R_a = \frac{1}{L}\int_0^L |Z(x)|\, dx$$

Root mean square (RMS) roughness R_q is the root mean square average of the roughness profile ordinates.

$$R_q = \sqrt{\frac{1}{L}\int_0^L Z^2(x)\, dx}$$

where L is the sampling length (diameter of the tablet), Z(x) represents the vertical deflections (in the z-direction) at each traced point (x) along the sampling length.

2.3 Results and Discussion

2.3.1 Effect of Layer Forces on the Interfacial Strength of Bilayer Tablets made of Plastic Material

% RSD of the breaking force of all the triplicates tested in study ranged from 1.4 to 3.6. To evaluate the impact of first and second layer forces on the mechanical strength of the tablets and on the mode of crack propagation different force combinations and layer (material) sequences were selected. Bilayer tablets made of avicel delaminated immediately after their compaction at first layer forces greater than 2 kN.

Figure 2-2 is the force-displacement plot of the avicel/avicel tablets made with constant second layer force of 10kN and with three different first layer forces (0.25, 0.5 and 1kN). Results imply that interfacial strength of bilayer tablets decreased with the increase of first layer force. Bilayer tablet made with first layer force of 0.25kN fractured in the top layer (though very close to the interface) all other tablets fractured along the interface. Bilayer tablets made with first layer force of 2kN or greater delaminated immediately after the compression. This indicates that the deformation history of the compacted material, i.e., the amount of plastic deformation in the first layer has a significant impact on the strength of the interface. Figure 2-4 displays the force-displacement plot of the tablets made with constant first layer force of 2kN and with three different second layer forces (15, 20 and 25kN). Results indicate that strength of the interface increased with the

increase of second layer force. It appears from the above results that the interfacial strength of the bilayer tablets made of plastic material is a function of both the first and second layer compaction stress, the magnitude of the layer forces will govern the degree of deformation endured by the particle assembly.

At higher first layer forces ($\geq$ 2kN), bilayer tablet made of plastic material delaminated immediately after the ejection from the die. This phenomenon can be attributed to the reduction in the interfacial roughness and also to the differences in the local stress history of the particles present in the adjacent layers. This is thought to be created from the presence of strain energy gradient across the interface [8]. The non-uniform expansion of the two adjacent layers will result in the development of a shear stress which will act on the interfacial zone between the two adjacent layers in contact. If the energy dissipation exceeds the magnitude of the energy contained within the adhesive bonds or junctions (provided by the interfacial roughness) between the particles the material will fracture and a crack will form [8].

Figures 2-3 and 2-5 show the roughness profiles of the bottom layer (first layer) of the fractured bilayer tablets. X- axis represent the length (along the diameter of the tablet) traversed by the stylus of perthometer and Y-axis represent the vertical deflections of the stylus as it traverses along the surface of the tablet. The surface roughness parameters, average roughness (R_a) and RMS roughness are extracted from the roughness profiles. As can be seen in table 1, the R_a and RMS roughness decreased with the increase of first layer force for tablets made with constant second layer force. Results summarized in table

2 indicate that for the tablets made with constant first layer force, R_a and RMS roughness values increased with the increase of second layer force. This effect is caused by the smoothening of the asperities present at the surface of the first (bottom) layer. If the valleys between the asperities on the surface are of the order of the size of individual particles they can provide sites for interlocking [25]. This mechanism not only increases the contact area between the particles of the adjacent layers at the interface but also promotes mechanical strengthening by interlocking of particles. Mechanical interlocking will result in the interface rupture path between the two layers becoming more tortuous, thus requiring a greater force to fracture the interface. Figure 2-6 indicates that the interfacial strength of the bilayer tablets made of plastic material increased with the increase of RMS roughness (an indication of interfacial tortuosity).

It is evident from Figure 2-3 that curvature of the roughness profiles varies with the first layer force. Roughness profiles tend to flatten out with the increase of first layer force. The reduced deformation of the first layer is due to the loss of the plasticity of the first layer material with the increase of the first layer force. For the tablets made with constant first layer force, interfacial curvature increased as the second layer force increased (Figure 2-5). This effect is due to the increased deformation of the interface with the increase of second layer force.

The applied compressive stress acts primarily in a downward central direction resulting in greater particle deformation in the lower central region of the die than at the outer radial regions. This phenomenon is due to the wall friction which retards the vertical movement

of the particles in contact with the die [26]. An important consequence of the postulated stress pattern that develops during the bilayer tablet compaction cycle is the curvature at the interfacial plane between the two adjacent layers. The interfacial curvature seems to be a direct result of the stress field created in the bulk particulate assembly under load. The deformation of the first layer increases the contact area between the two layers available for bond formation and also opens the possibility of other strength increasing mechanical mechanisms such as particle interlocking. Magnitude of the interfacial curvature indicates the depth of penetration of top layer into the bottom layer.

2.3.2 Effect of Layer Forces on the Strength of Bilayer Tablets made of Brittle Material

As observed for bilayer tablets made of plastic material, the strength of bilayer tablets made of brittle material decreased with the increase of first layer force (Figures 2-7 and 2-9). For the bilayer tablets made of brittle material, delamination has not occurred even at the first layer force of 6 kN (second layer force being 10kN), but bilayer tablets made of plastic material with first layer force greater than 2 kN (10 kN second layer force) delaminated immediately after ejection from the die. The other major difference observed for the tablets with both these materials is the mode of breakage, in the case of bilayer tablets made of brittle material fracture has occurred in the first (bottom layer) indicating that interfacial strength is greater than layer strength. In the case of bilayer tablets discussed above breakage has occurred along the interface, implying that layer(s) strength is higher than interfacial strength. Application of load on the bilayer tablet during axial testing will allow crack to propagate to the region of weaker strength in the tablet. If interfacial strength is weaker than layer strength fracture occurs at the interface and *vice*

versa [25]. Karehill et al. [16] have demonstrated that volume reduction by fragmentation (the consolidation mechanism of brittle materials) seems to be a more efficient means of producing larger surface areas that would promote bonding between particles in the tablets.

Figure 2-8 shows that for the bilayer tablets made of brittle material with the increase of first layer force propagation of crack has occurred closer to the interface, indicating that strength of first layer increases with the increase of first layer force. It is evident from this phenomenon that as a function of first layer force regional strengths shift within the bilayer tablets. Interfacial roughness cannot be measured for these tablets as the fracture has not occurred at the interface.

2.3.3 Effect of Layer Sequence on the Strength of Bilayer Tablets

Figure 2-10 shows the force-displacement plots of the bilayer tablets made with two different layer sequences (avicel/lactose & lactose/avicel). All the tablets were made with same first layer force (0.5 kN), and each layer sequence was compacted with two second layer forces (10kN and 20kN). All the tablets under axial loading have fractured along the interface, except for the avicel (0.5kN)/lactose (20kN) tablet, for this tablet crack has propagated into the second layer, implying that interfacial strength is greater than layer strength. As seen from the force-displacement curves in the (Figure 2-10), for tablets made with same second layer force (and different layer sequence) interfacial strength is higher for the tablets with brittle material in the first layer. For tablets made with identical

layer sequence (and different second layer force), interfacial strength increased with the increase of second layer force.

All tablets are made with constant first layer force (0.5 kN) and varying second layer force. Interfacial roughness profiles (Figure 2-11) of the tablets fractured along the interface were obtained using Perthometer. Values of Average roughness (R_a) and RMS roughness of the bottom layer are tabulated in table 3.

Curvature of the roughness profiles is higher for bilayer tablets with plastic material in the first layer (second layer force being constant). The reason for this mechanism can be attributed to the plasticity of the first layer, plastic materials being more deformable compared to the brittle materials. Curvature of the profiles increased with the increase of second layer force for both the plastic and brittle materials in the first layer. A large second layer force increases the deformation of the first layer and results in a large curvature at the interfacial boundary. Particles present at the interface will have been greatly deformed by the predominant mechanism of plastic flow and hence a large region of contact area will available for bond formation between the two adjacent layers. The higher number of junctions coupled with an increase in the roughness of the interface will result in the propagation of the crack more energetically demanding [27]. For tablets made with brittle material in the first layer, average roughness (R_a) decreased with the increase of second layer force (Table 3). This is due to the smoothening of the interface at the higher second layer force. Results indicate that for the tablets made with different layer sequence and same force combination, interfacial roughness is higher for the tablets made with brittle material in the first layer. Due to the fracture of brittle particles new

surfaces are generated and provide contact points for the better particle-particle interlocking.

2.3.4 Effect of Lubricants on the Strength of Bilayer Tablets

Two levels of magnesium sterate (0.25% and 0.75%) were investigated to understand their impact on the interfacial strength of the tablets. As shown in the Figure 2-12, for the bilayer tablets made of plastic material with same second layer force (10kN) and two different first layer forces (0.25 and 0.5kN), strength of tablets decreased substantially with the increase in amount of lubricant for both the first layer forces. Same trend was observed for the tablets made with brittle materials (Figure 2-13). Effect of lubricant (i.e. reduction in tablet strength with the increase of lubricant concentration) on the tablet strength is higher for the bilayer tablets made of plastic material as compared to the bilayer tablets made of brittle material. Breakage has occurred along the interface for the tablets made of plastic material and for the tablets made of brittle material breakage was observed in the first layer. The above observed phenomenon can be attributed to the reduced friction between powder particles with the increase of lubricant concentration [23]. It is known that increased lubricity results in the weaker interfaces for tablets made of plastic material and reduced layer strength in the case of brittle tablets.

2.4 Conclusions

Strength of bilayer tablets was characterized using an axial tester. It was observed that upon axially loading the tablets, crack has propagated along the interface for tablets made of plastic material. In the case of brittle materials, breakage was observed in the first

layer. The observed differences in the crack propagation modes can be attributed to the relative strengths of interface and individual layers, as crack will propagate into regions with weaker structural integrity upon loading. In the case of tablets made of plastic material individual layers are stronger than interface so the fracture occurred along the interface, where as in the case of tablets made of brittle material interfacial strength dominated the layer strength so the fracture was observed in the first layer. These differences can be attributed to the differences in the consolidation mechanisms of both the materials.

Stylus based perthometer was found to be a robust method for quantifying the interfacial roughness of the fractured tablets. A strong correlation was found between the roughness parameters R_a (average roughness), R_q (RMS roughness) and the strength of bilayer tablets. Strength of bilayer tablets increased with the increase of interfacial roughness. It was observed that both the first and second layer forces determined the magnitude of interfacial roughness for both the plastic and brittle materials.

Material properties and layer forces have strongly influenced the magnitude of interfacial curvature developed at the interface during the compaction. Interfacial roughness along with the interfacial curvature provided the mechanical interlocking of the adjacent layers and hence determined the interfacial strength of tablets.

Layer sequence along with compaction forces played a key role in influencing the strength of bilayer tablets. For the same (first & second layer) force combination,

interfacial strength was higher for the tablets with brittle material in the first layer. This effect can be attributed to the consolidation mechanism brittle material, which deforms by fragmentation. As a result of brittle fracture more active sites were available for mechanical interlocking of the adjacent layers, and hence produced a stronger interface. For the same layer sequence, interfacial strength increased with the increase of second layer force. Increasing the second layer force deformed the interface to a greater extent enabling the second layer to penetrate into the first layer thus increasing the bonding strength of the interface. Interfacial strength was influenced both by the tortuosity of the interface and by the deformation of the interface due to plastic flow.

It was observed that concentration of the lubrication played a key role in influencing the strength of the bilayer tablets. For both the plastic and brittle materials, tablet strength decreased with the increase of lubricant concentration. Effect of lubricant (i.e. reduction in tablet strength with the increase of lubricant concentration) on the strength of tablets is higher for tablets made of plastic material as compared to the tablets made of brittle material.

2.5 Figures for Chapter 2

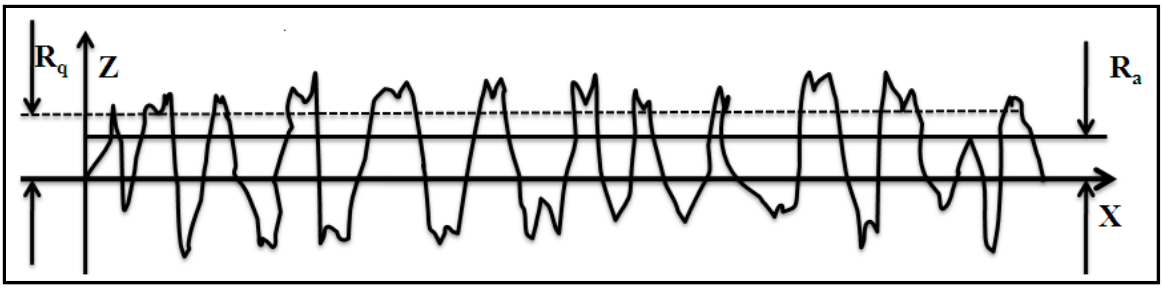


Figure 2-1: Schematic of a surface roughness profile.

Figure 2-2: Force-displacement plots of the bilayer tablets made of plastic material (avicel/avicel) with varying first layer and constant second layer force.

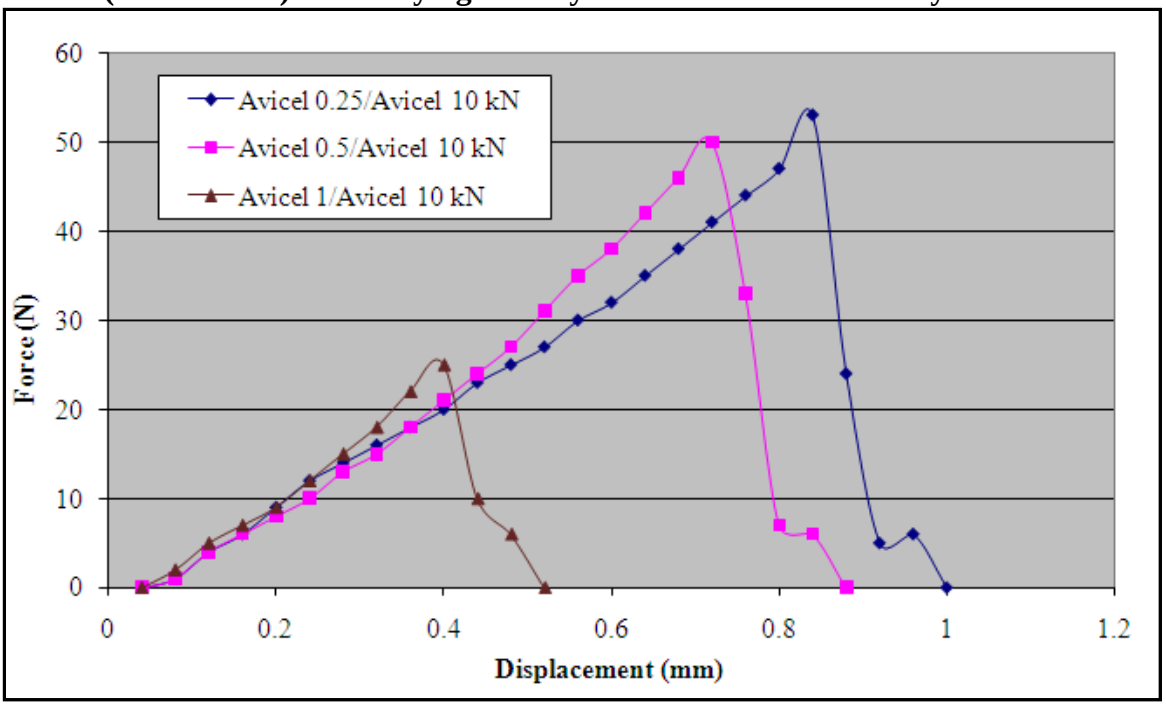


Figure 2-3: Roughness profiles of the interfacial fracture surfaces of the first layer of the bilayer tablets (avicel/avicel) compressed with different first layer forces.

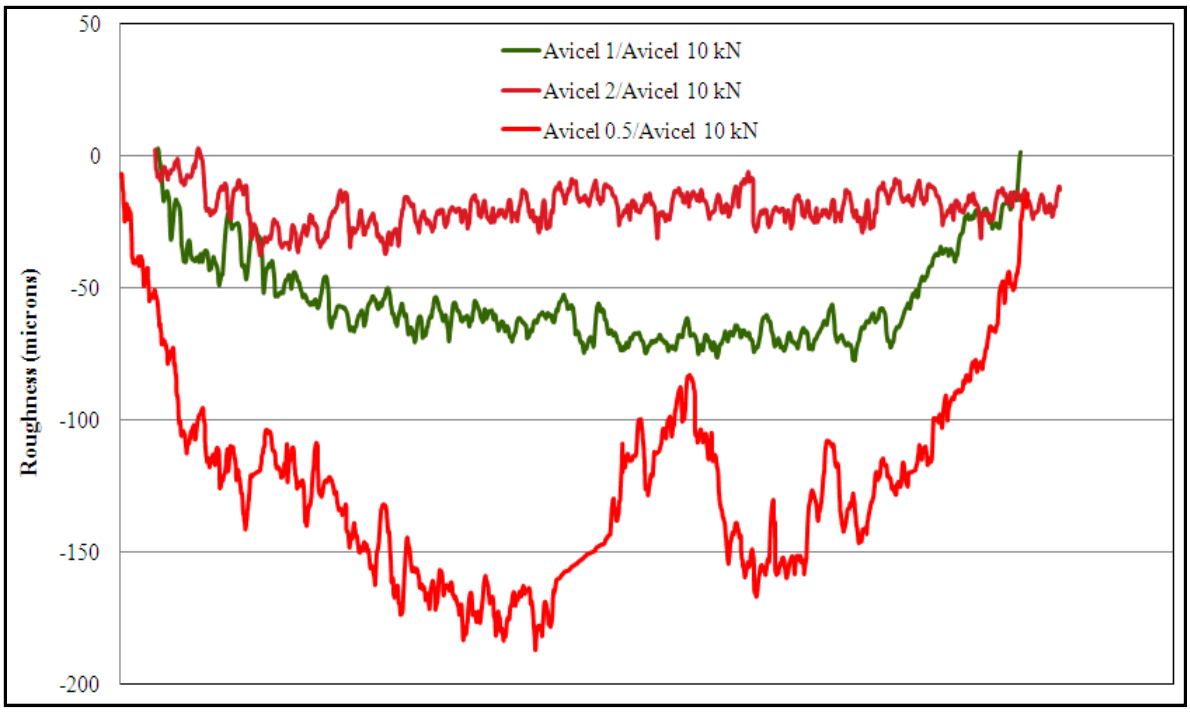


Figure 2-4: Force-displacement plots of the bilayer tablets made of plastic material (avicel/avicel) with constant first layer and varying second layer force.

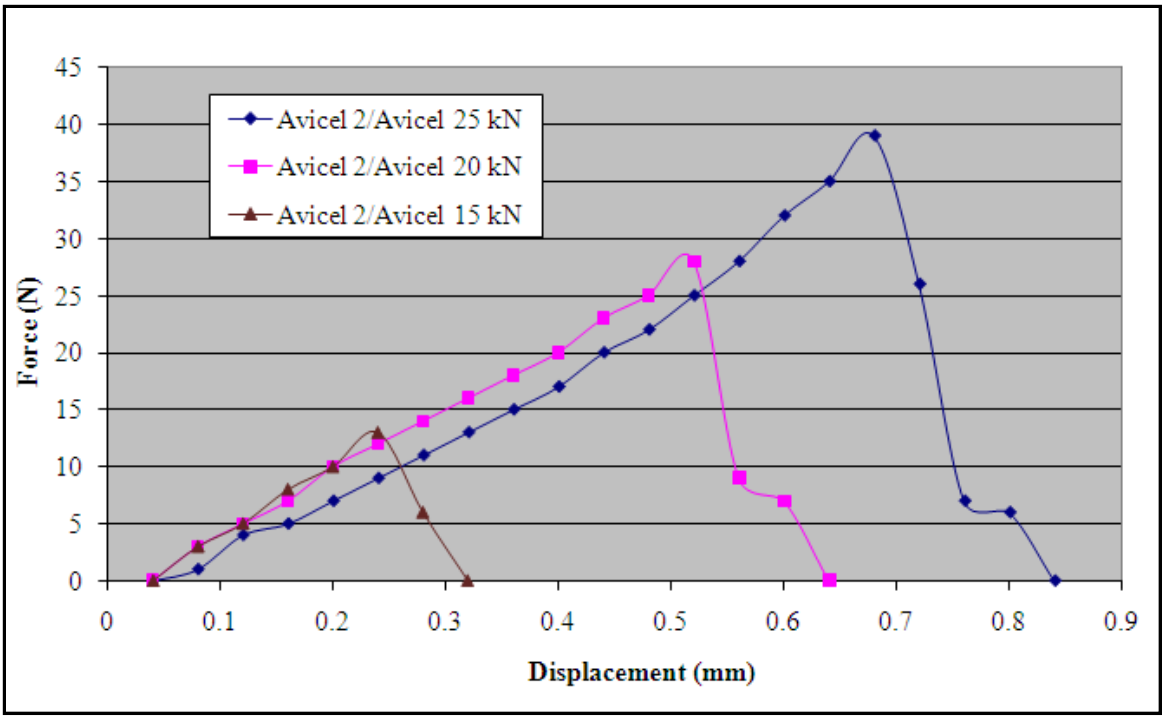


Figure 2-5: Roughness profiles of the interfacial fracture surfaces of the first layer of the bilayer tablets (avicel/avicel) compressed with different second layer forces.

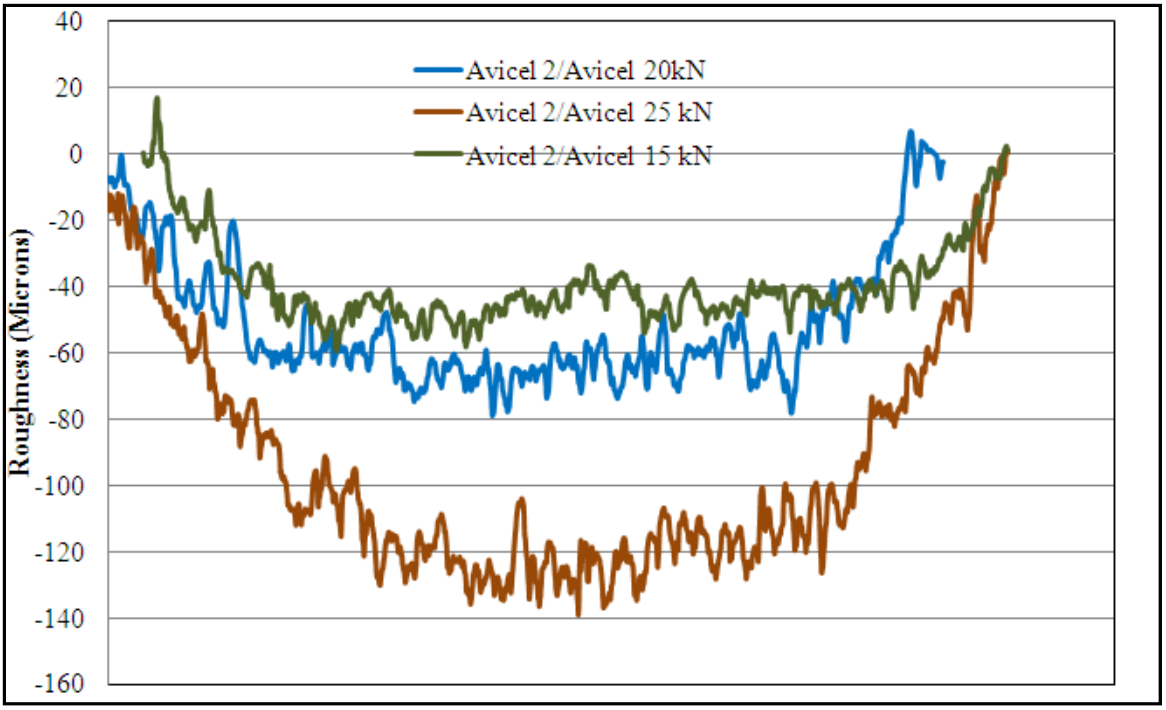


Figure 2-6: Effect of interfacial root mean square (RMS) roughness on the strength of the bilayer tablets made of plastic material (avicel/avicel).

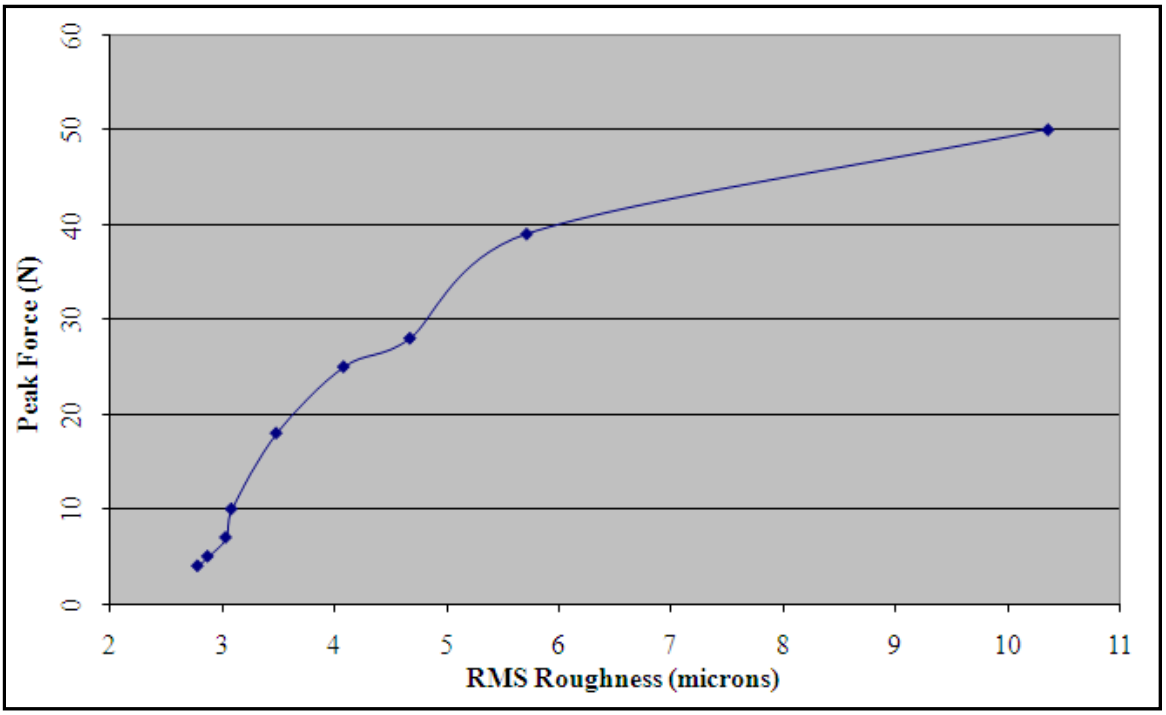


Figure 2-7: Force-displacement plots of the bilayer tablets made of brittle material (lactose/lactose) with varying first layer and constant second layer force.

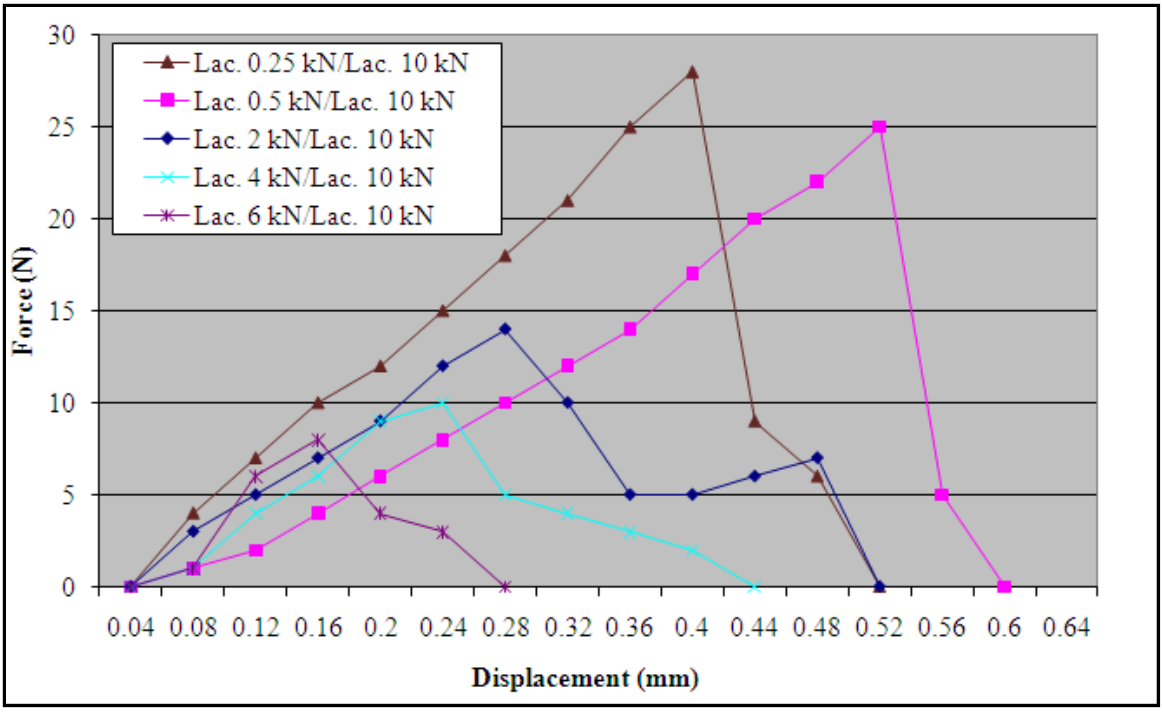


Figure 2-8: Crack propagation modes in the tablets made of brittle material (lactose/lactose) made with constant second layer force and varying first layer force.

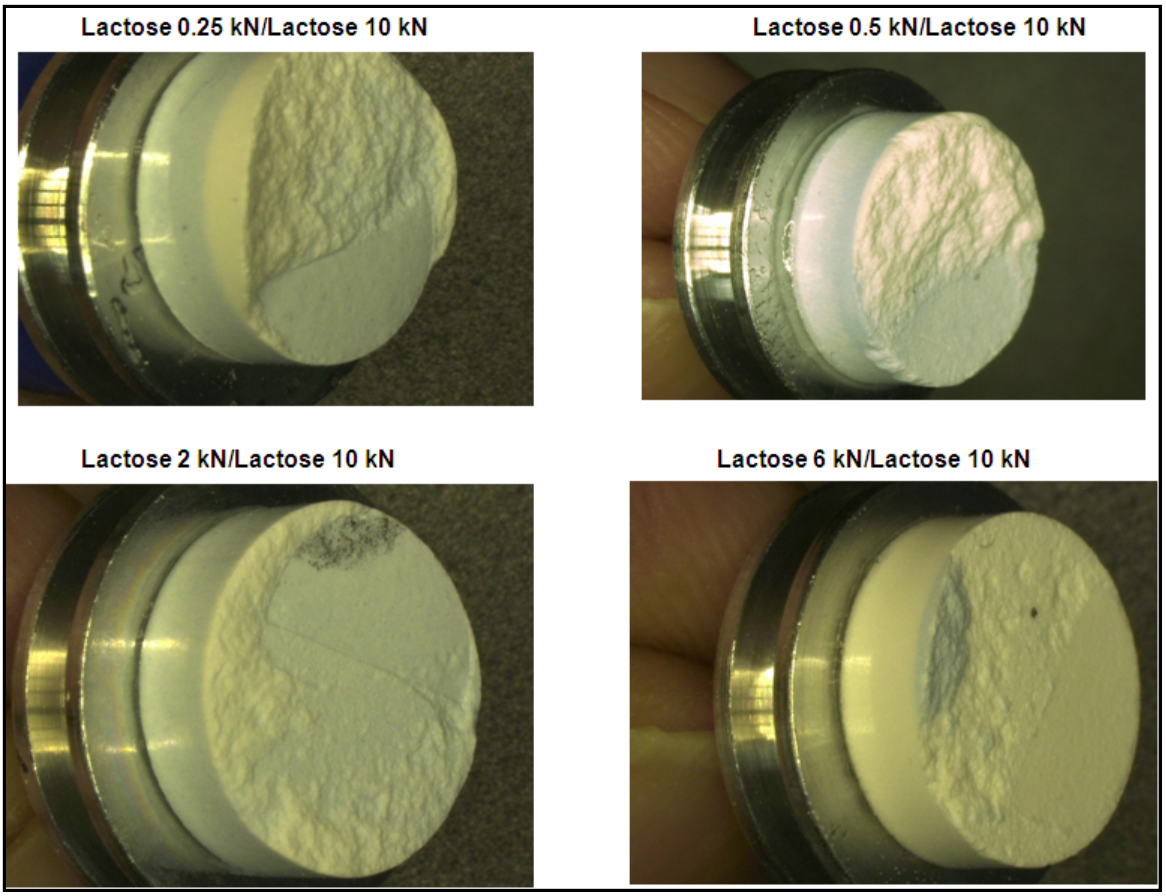


Figure 2-9: Effect of first layer force on the strength of the bilayer tablets made of brittle (lactose/lactose) material.

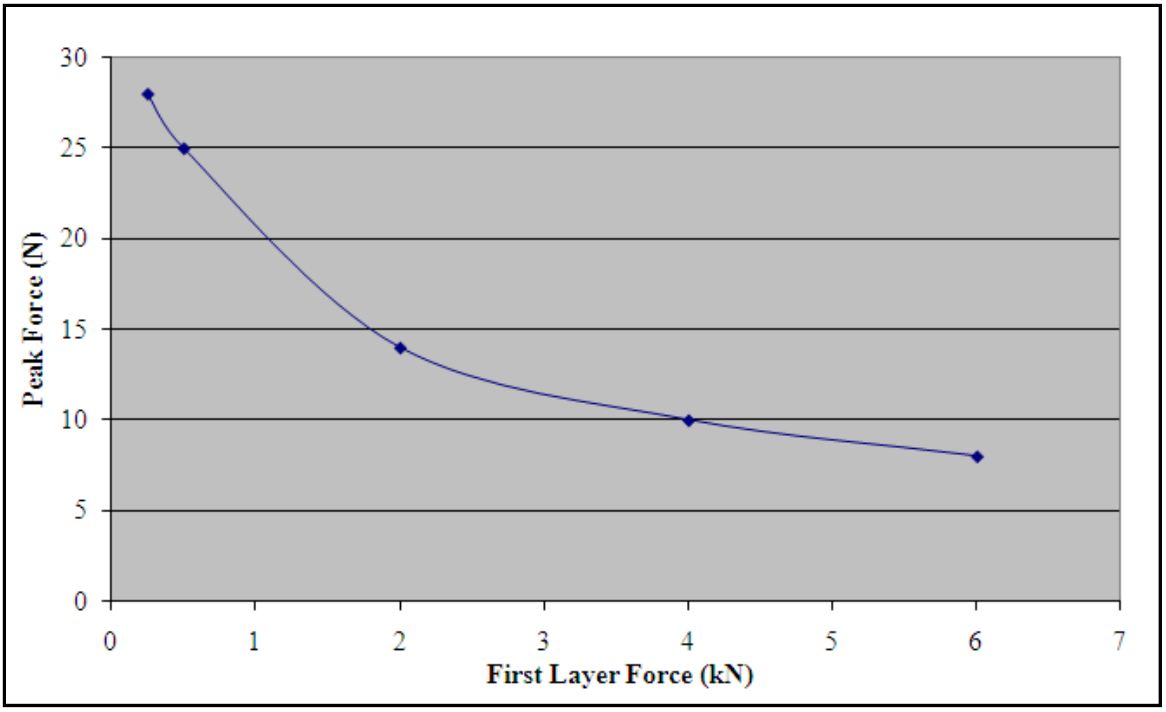


Figure 2-10: Force-displacement plots of the compacts made with different layer sequences and with constant first layer and varying second layer force.

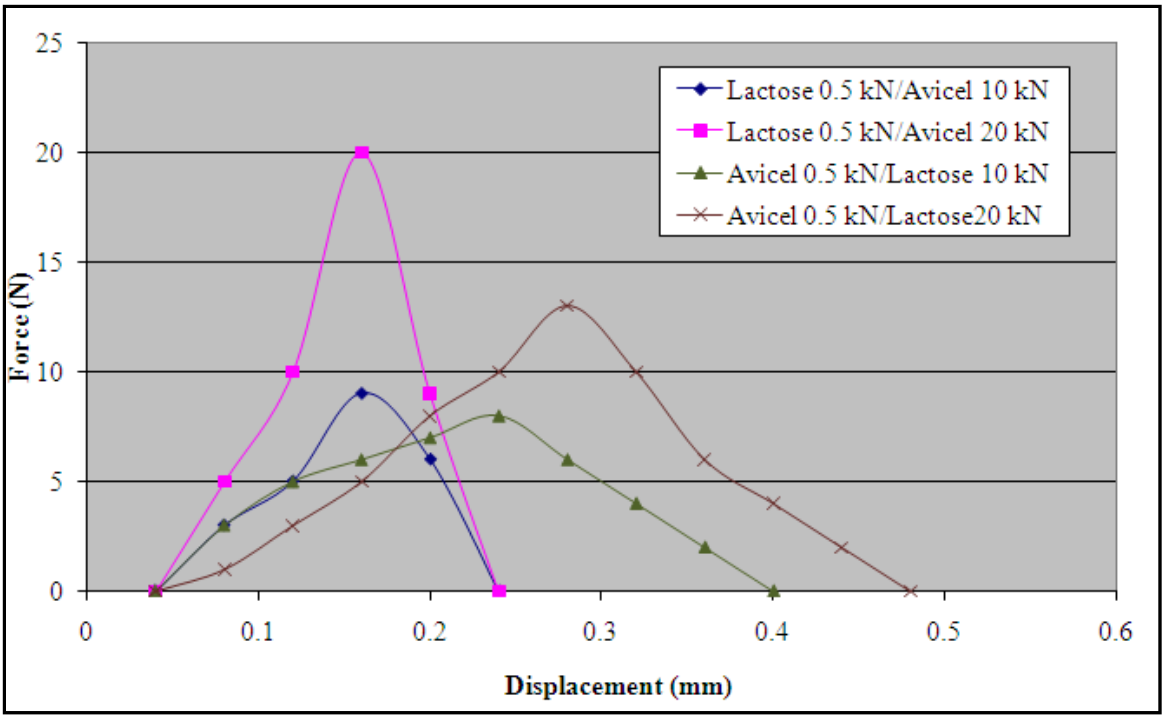


Figure 2-11: Roughness profiles of the interfacial fracture surfaces of the first layer of the bilayer tablets made with different layer sequences and with constant first layer and varying second layer force.

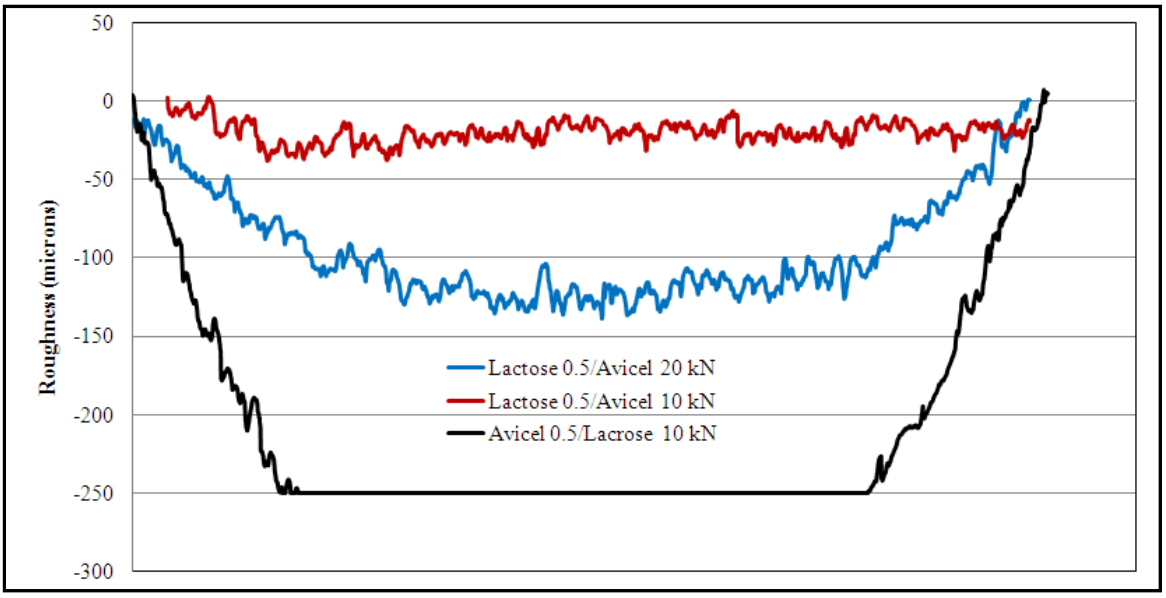


Figure 2-12: Effect of lubricant concentration on the strength of bilayer tablets made of plastic material (avicel/avicel).

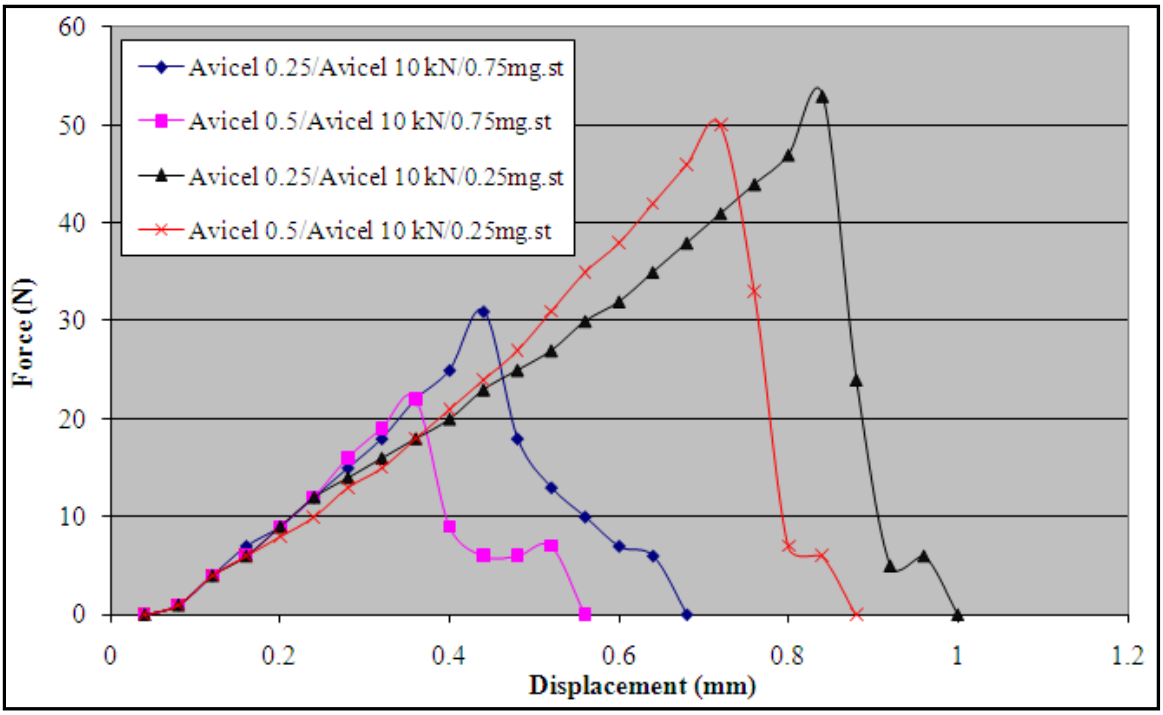
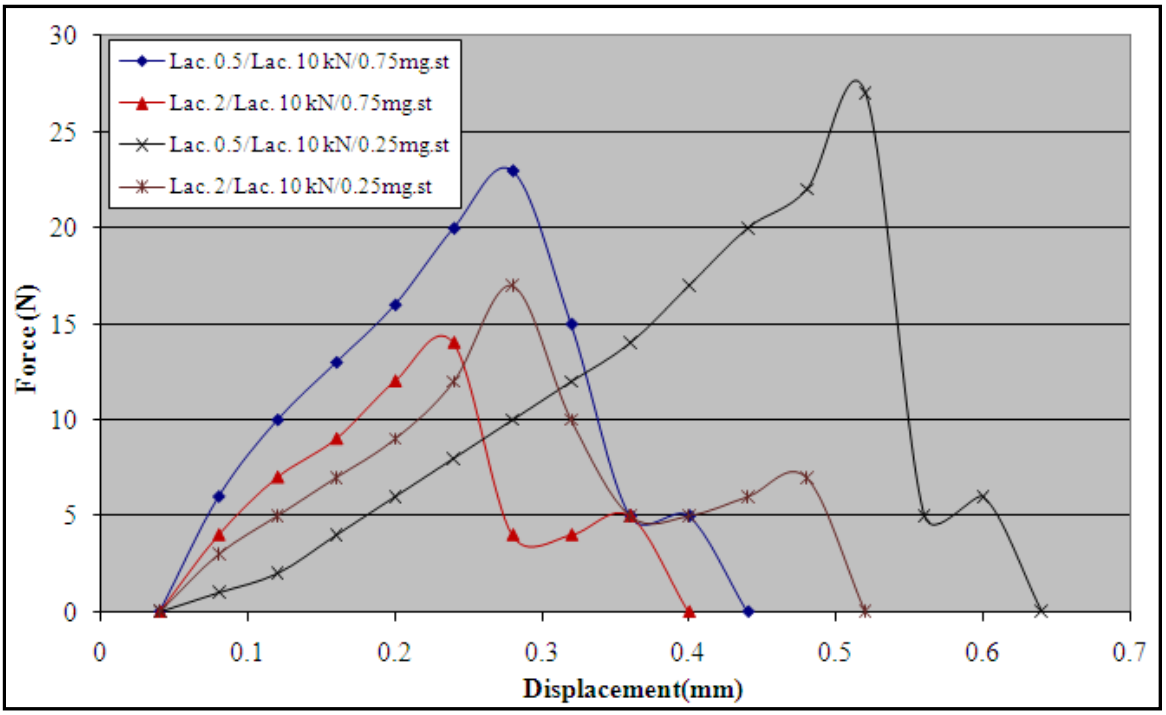


Figure 2-13: Effect lubricant concentration on the strength of tablets (lactose/lactose) made of brittle material (lactose/lactose).



2.6 Tables for Chapter 2

Table 2-1: Roughness parameters of the interfacial fracture surfaces of the first layer of tablets made of plastic material. These tablets were compressed with constant second layer force (10 kN) while varying first layer force.

First Layer	Second Layer	Ra (microns)	Rq (microns)
Avicel 0.25 kN	Avicel 10 kN	Not available due to layer breakage.	
Avicel 0.5 kN	Avicel 10 kN	5.11	8.49
Avicel 1 kN	Avicel 10 kN	4.12	6.46
Avicel 2 kN	Avicel 10 kN	3.73	4.98

Table 2-2: Roughness parameters of the interfacial fracture surfaces of the first layer of tablets made of plastic material. These tablets were compressed with constant first layer force (2 kN) while varying second layer force.

First Layer	Second Layer	Ra (microns)	Rq (microns)
Avicel 2 kN	Avicel 15 kN	4.42	5.62
Avicel 2 kN	Avicel 20 kN	6.92	9.46
Avicel 2 kN	Avicel 25 kN	7.24	10.35

Table 2-3: Roughness parameters of the interfacial fracture surfaces of the first layer of bilayer compacts made with different layer sequences.

First Layer	Second Layer	Ra (microns)	Rq (microns)
Avicel 0.5 kN	Lactose 10 kN	2.18	2.72
Avicel 0.5 kN	Lactose 20 kN	Not available due to layer breakage.	
Lactose 0.5 kN	Avicel 10 kN	2.58	2.87
Lactose 0.5 kN	Avicel 20 kN	4.17	5.97

Chapter 3: Application of Fracture Mechanics for the Characterization of Bilayer Tablets

3.1 Background

In the pharmaceutical industry the process of bilayer design is heavily dependent on the trial-and-error approach during the formulation, process development, and at scale-up stages. To overcome this hurdle it is critical to understand the mechanical properties of the materials and to develop a methodology for the characterization of bilayer compacts.

Pharmaceutical powders used in tableting vary in their deformation characteristics from those that are brittle and consolidate by particle fragmentation to those that are ductile and consolidate by plastic flow [28]. Several studies were carried to understand the deformability of pharmaceutical powders. These studies used work done during compaction and pressure/volume relationships obtained using instrumented presses. One such study [29] of characterizing the mechanical behavior of powders is to determine the resistance to deformation by measuring the change in volume during compaction. Although these techniques give an indication of the scale of deformability of materials, they do not provide the definitive mechanical constants describing the brittleness (fragmentation propensity) and ductility (the ability to deform by plastic flow) [29]. Brittleness is the key property of pharmaceutical powders [30]. According to York et al. [31], brittleness of pharmaceutical compacts is a result of little or no plastic deformation before fracture, since no significant dislocation motion is possible in the material to allow overall plasticity. The stress intensity factor (K_I) is a measure of the brittleness of materials [32]. It quantifies the stress field near the crack tip and hence describes the

resistance offered by the material to crack propagation. According to Podczeck [28], crack propagation and the theory of fracture mechanics are of the utmost importance for understanding the mechanisms of adhesion and friction between individual powder particles.

Mashadi and Newton [12] estimated the critical stress factor (K_{IC}) for Avicel 101 (micro-crystalline cellulose) beams made at different porosities. Results of their studies indicated that the value of K_{IC} decreased with the increase in tablet porosity, i.e. less resistance is offered to crack propagation. They have also observed that, even though Avicel 102 with its low Young's modulus is similar to ductile polymeric materials in terms of its rigidity; its brittleness is similar to that of ceramic materials in terms of crack propagation, as indicated by its critical strain energy release rate and fracture toughness. Roberts and Rowe [32] determined the K_{IC} of microcrystalline cellulose (MCC) based on the fracture of radially edge cracked tablets using the techniques of edge opening and diametrical compression. Of these two techniques edge opening was preferred, since it gave the most stable crack propagation and the effects of crack length were minimal. However, the diametrical compression test was found to have provided valuable results within a certain range of crack length. Podczeck [28] investigated the impact of porosity on the critical stress intensity factor of acetylsalicylic acid and lactose monohydrate tablets subjected to mode III loading (tearing or antiplane shear mode). Experimental results indicated that acetylsalicylic acid undergoes different deformation mechanisms at different porosities. In contrast, Young's modulus, tensile strength, and critical stress intensity factor of lactose monohydrate beams were found to relate to the beam porosity exponentially.

Phani and Niyogi [33] have also extensively examined the relationships between the mechanical properties of materials as a function of their porosities. Wiederhorn [34] investigated the influence of water vapor on crack propagation in soda-lime glass and found that critical stress intensity factor (K_{IC}) decreased with the increase in the amounts of water vapor. Jeronimidis [35] found that for wood fractured along the grain water vapor caused an increase in the fracture toughness.

The above referenced studies were carried out on single layered beams or tablets (of homogenous material) and they have focused on the impact of porosity on the mechanical properties of tablets. With respect to the determination of stress intensity factor, in some of the above references the crack length and orientation of the crack was not mentioned or not controlled. In addition, extrapolations to zero porosity values often suffered from a lack of data close to zero porosity.

The objective of this chapter is to apply the fracture mechanics principles to characterize the bilayer tablets by understanding the interplay of physico-mechanical properties of the powders and compression process parameters. As part of this endeavor, a methodology was developed to estimate the stress intensity factor of bilayer interfaces (K_I). To determine the (K_I), bilayer tablets were manufactured by introducing the crack (semi-circular shaped) of known dimensions at the interface of the adjacent layers. Cracks in brittle tablets are most likely to propagate under the influence of tensile stresses, and brittle cracks will always seek an orientation that minimizes the shear loading. Mode I of crack-surface displacement is therefore essential for the characterization of brittle tablets.

In this study we have axially loaded the bilayer tablets (using an axial tester). The above mentioned bilayer configuration and testing methodology will facilitate the estimation of the stress intensity factor (K_I) of the bilayer interface.

Investigations were also carried out to understand: i) the dependency of stress intensity factor on interfacial radius of curvature and roughness, ii) the effect of deformation history of the first layer and second layer forces on the interfacial stress intensity factor of plastic and brittle materials, and iii) the impact of material properties and layer sequence on the interfacial stress intensity factor.

3.2 Materials and Methods

3.2.1 Theory: Fracture Mechanics

Brittleness is the characteristic feature of pharmaceutical powder tablets, which means that fracture is not preceded by significant deformation [36]. Hence, fracture mechanics can describe the mechanical failure of tablets. According to Griffith's hypothesis [37], for a crack to grow under static loading two conditions are essential. Firstly stress must be high enough to initiate fracture and secondly, the energy released by crack growth must be equal to the energy required to form new surfaces. The stress intensity factor is the stress field intensity at the tip of a crack and is a function of the applied load and the test piece geometry. In order to apply continuum stress analysis for plane-cracks in specimens such as bilayer tablets, three basic modes of crack-surface displacements are considered. Mode I (the opening or 'tensile' mode), corresponds to the normal separation of crack walls under the action of tensile stresses; Mode II (the sliding or 'in-plane shear'

mode) corresponds to longitudinal shearing of the crack walls in a direction normal to the crack front; and Mode III (the tearing or 'anti-plane shear' mode) which corresponds to a lateral shearing parallel to the crack front. These three basic modes of loading are shown in Figure 3-1.

3.2.2 Estimation of Interfacial Stress Intensity Factor (K_I)

Williams [38] evaluated the nature of the stress and displacement fields arising very close to the tip of an interface crack present in between elastically dissimilar media. It was assumed that the crack is open (under remote tension), right up to the tip. This gives rise to a stress field which is oscillatory in nature [39], with stress varying as

$$\sigma_{ij}\ \alpha\ r^{-\frac{1}{2}}\cos\left(\varepsilon \log r\right)$$

For small distances from the crack tip (r), the "bi-elastic constant" (ε), is related to the elastic constants of the two bonded solids by

$$\varepsilon = \frac{1}{2\pi}\log\frac{(1+\beta)}{(1-\beta)}$$

In the above equation β represents Dundurs' parameter. For a bi-material joint β depends on modulus of rigidity (μ_1, μ_2) and Poisson's ratio (υ_1, υ_2) of material (layer) 1 and material (layer) 2. Dundurs' parameter is obtained by the following expression.

$$\beta = \frac{\mu_2\,(\alpha_1 - 1) - \mu_1(\alpha_2 - 1)}{\mu_2\,(\alpha_1 + 1) + \mu_1(\alpha_2 + 1)}$$

Where α is Kolosov's constant in plane strain condition.

$$\alpha_i = 3 - 4\vartheta_i$$

The complex interfacial stress intensity factor K, is a function of K_I and K_{II} (stress intensity factors for cracks in an infinite body loaded in modes I and II). For a uniform remote loading at infinity, the interfacial stress intensity factor is given by following expression:

$$K = K_I + iK_2 = \left[\sigma_{yy}^{\infty} - i\sigma_{xy}^{\infty}\right]\sqrt{\frac{\pi L}{2}}\ (1 - 2i\varepsilon)L^{i\varepsilon}$$

In this study we have considered only K_I (mode I loading) of interfacial (edge) cracks, as cracks in the tablets made of brittle material are most likely to propagate under the influence of tensile stresses. Separation of the above complex expression into real and imaginary parts will yield K_I and K_{II}.

For mode I loading

$$K_I = \sigma_{yy}\sqrt{\frac{\pi L}{2}}\ [\cos(\varepsilon \times \ln L) + 2\varepsilon \sin(\varepsilon \times \ln L)]$$

Where L represents crack length and σ^{∞}_{yy} is the remote peak tensile load.

Even though bilayer tablets are loaded axially, due to the interfacial roughness, orientation of crack front, and due to the slight misalignment of loading arms during the axial testing shear stresses will be generated at the interfacial zone. As a result of this, K_{II} might exist and due to this crack growth might be mixed mode. Estimation of K_{II} for bilayer interfaces is beyond the scope of this dissertation and determined in the future studies. In the future studies it will be also worthwhile to estimate the phase angles of the interfacial cracks using K_I and K_{II} values. This will allow in predicting the kinking of bi-material interfacial cracks.

3.2.3 Materials

The materials and method used to prepare the bilayer tablets is same as described in chapter 2.

3.2.4 Bilayer Tablet Testing

The semi-circular shaped aluminum foil at the interface covers half the surface of the interface and acts as a crack (Figure 3-2). This configuration allows us to estimate the stress intensity factor (K_I) of the interface. The rationale for introducing a dominant flaw (large crack) at interface is to reduce the influence of discontinuities due to the presence of micro-cracks and pores in the compacts (i.e. preventing them from propagation after axially loading the tablets). Breaking force (or axial strength) of the bilayer compacts was determined by the axial tester (MARK-10 Corporation, Copiague, NY). Bilayer tablets were individually glued to two tablet holders (Figure 3-3) using a cyanoacrylate based glue (LOCTITE®, Henkel Corporation, Avon, OH) and left for an hour to ensure a good adhesion [25]. Tablet 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 catastrophic fracture of the bilayer tablet. Fracture forces (obtained from the force-displacement plots) and measured diameters of the tablets was used to calculate the remote peak tensile load of the tablets using

$$\sigma_{yy}^{\infty} = \frac{F}{A_{effective}}$$

where F is the peak force obtained from the force-displacement curves of the axial testing and $A_{effective}$ is the area of the bilayer interface not covered by the semi-circular crack.

3.3 Results and Discussion

The first step of this study was to evaluate the variation of stress intensity factor along the crack front of a straight fronted crack in a cylindrical bar under tensile loading. For this purpose numerical solutions obtained by Carpinteri [40] were used to obtain SIF values at the crack center A and at the crack end B (bar surface) as shown in the Figure 3-4. Dimensionless SIF Y in Mode I loading depends on the crack depth (ratio of crack length to tablet diameter), the crack aspect ratio and the position of the considered point at the crack front. SIF values at the crack center A and at the crack end B are obtained by the following equations:

$$Y_A = 0.67 - 0.033\left(\frac{a}{b}\right) + 5.73\left(\frac{a}{D}\right) - 0.29\left(\frac{a}{b}\right)^2 - 2.943\left(\frac{a}{b}\right)\left(\frac{a}{D}\right) - 22.692\left(\frac{a}{D}\right)^2 + 2.41\left(\frac{a}{b}\right)^2\left(\frac{a}{D}\right) + 10.684\left(\frac{a}{b}\right)\left(\frac{a}{D}\right)^2 + 49.34\left(\frac{a}{D}\right)^3 - 8.82\left(\frac{a}{b}\right)^2\left(\frac{a}{D}\right)^2 - 10.16\left(\frac{a}{b}\right)\left(\frac{a}{D}\right)^3 - 21.43\left(\frac{a}{D}\right)^4$$

$$Y_B = 455 - 0.233\left(\frac{a}{b}\right) + 4.893\left(\frac{a}{D}\right) + 0.113\left(\frac{a}{b}\right)^2 + 0.197\left(\frac{a}{b}\right)\left(\frac{a}{D}\right) - 21.03\left(\frac{a}{D}\right)^2 + 0.557\left(\frac{a}{b}\right)^2\left(\frac{a}{D}\right) + 3.134\left(\frac{a}{b}\right)\left(\frac{a}{D}\right)^2 + 49.497\left(\frac{a}{D}\right)^3 - 5.415\left(\frac{a}{b}\right)^2\left(\frac{a}{D}\right)^2 - 1.124\left(\frac{a}{b}\right)\left(\frac{a}{D}\right)^3 - 24.702\left(\frac{a}{D}\right)^4$$

In the above equations a/D represents the crack depth and a/b is the crack aspect ratio. For straight fronted cracks, the crack aspect ratio is zero. Dimensionless SIFs were computed for all the tablets made with different materials, layer forces, and layer sequences as part of this study. The results indicated that SIF remained almost constant at the crack center and at the crack end for all the tablets. The largest difference between the SIFs Y_A (crack center) and Y_B (crack end) was found for the avicel PH-102 (0.25kN)/lactose (20kN) tablet. For this tablet Y_A = 1.766 and Y_B = 1.416. This shows that variation of the SIF along the crack front is minimum; hence it is reasonable to consider that the SIF is constant along the crack front.

3.3.1 Effect of Layer Forces on Stress Intensity Factor (K_I)

Bilayer tablets of brittle and plastic materials were made with constant second layer force of (10 and 20 kN) and varying first layer forces. As shown in Figures 3-5 and 3-6, for both the plastic and brittle tablets made at a constant second layer force, SIF decreased with an increase in first layer force.

The results have also indicated that for plastic bilayer tablets made with first layer force $\leq$ 0.5kN; SIF is higher for tablets made with lower second layer force. This phenomenon

can be attributed to the consolidation mechanism of plastic materials. As they consolidate by virtue of plastic deformation, increasing the second layer force will smoothen the asperities present at the surface of the first (bottom) layer [16]. This will reduce the mechanical interlocking of the adjacent layers and hence the reduction in the resistance offered by the interface for the crack propagation. But this trend reverses with the increase of first layer force beyond 0.5 kN (i.e. SIF is higher for tablets made with higher second layer force). Interfacial roughness will decrease with the increase in first layer force for tablets made of plastic material and this will reduce the strength of the interface, but by increasing the second layer force there will be a greater penetration of second layer into the first layer (this is reflected by the interfacial curvature) and this will strengthen the interface by interlocking of two layers [16]. This effect is reflected in the increase of interfacial SIF.

Whereas in the case of brittle bilayer tablets SIF is higher for tablets made with higher second layer force (at first layer force $\leq$ 0.5kN) and this trend reverses with the increase of first layer force beyond 0.5 kN. This effect is due to the loss in the strength of lactose tablets at higher applied forces. Podczeck [28] estimated the anisotropy (ratio between the critical stress intensity factors obtained in mode I and mode III loading) values of lactose tablets and found that they exhibit a higher degree of anisotropy. This indicates a non uniform stress transmission through the powder column in axial and radial direction. At lower compact porosities this can lead to lamination of the tablet after ejection from the die [28]. Kikuta and Kitamori [41] observed a significant increase in the adhesive force between the lactose particles and the die walls with the increase of compression

force. The increased adhesion of lactose particles resulted in higher ejection force of the lactose tablets. Ejection of the tablet from the die at higher forces would have generated micro-cracks in the lactose tablet and would have weakened the mechanical strength that resulted in the lower SIF at higher compression forces.

3.3.2 Effect of Materials and First Layer Force on SIF (K_I)

As indicated in Figure 3-7, for both the plastic and brittle bilayer tablets made with constant second layer force of (10 kN) and varying first layer forces, the SIF factor decreased with an increase in first layer force. As observed from the results, for first layer forces $\leq$ 2kN, SIF of the bilayer tablets made of plastic material is higher than those made of brittle material. This effect is due to the deformability capacity of the particles on the first layer and this phenomenon is manifested in the form of interfacial radius of curvature due to the penetration of second layer into the first layer. Degree of penetration will be higher due to the retained plasticity at low first layer forces [42]. At first layer forces > 2kN, SIF of bilayer tablets made of brittle material is higher than those that of plastic material. This is due to the fragmentation of brittle materials at higher first layer forces and the resulting new particle surfaces on the interface which will act as nesting sites to promote resistance to interfacial crack propagation. For tablets made of plastic material with the increase of first layer force both the plasticity and interfacial roughness (which provides interlocking sites) are significantly reduced and this results in the weaker interlocking of the adjacent layers and hence the reduced resistance to the crack propagation.

Figure 3-8 shows that the SIF of bilayer tablets made of brittle and plastic material made at constant second layer force (20 kN) and with varying first layer forces. The results indicate that SIF of the tablets made of plastic material is always higher than those that of brittle material. This phenomenon can be attributed to the plastic flow during the compression of bilayer tablets. With the increase of the second layer force there is a greater degree of the deformation of the interface [42] and this will contribute to the increased mechanical interlocking of the layers and hence an increased SIF.

In the case of brittle materials increase of second layer force will weaken the tablet strength due to the generation of micro-cracks as a result of high ejection forces and residual die wall pressure due to the increased adhesion of lactose particles to the die wall [41]. This will weaken the strength of the tablet and hence a reduction in SIF was observed at larger second layer forces.

3.3.3 Effect of Layer Sequence and Second Layer Force on SIF

Figure 3-9 shows the SIF plots of the bilayer tablets made with two different layer sequences (avicel/lactose & lactose/avicel). Each layer sequence was compacted with varying first layer forces and two second layer forces (10kN and 20kN). The plots indicate that for tablets made with same second layer force the SIF is higher for the tablets with brittle material in the first layer. For tablets made with identical layer sequence (and different second layer force), the SIF increased with an increase in second layer force.

The observed phenomenon can be attributed to the interfacial roughness and the deformability of the first layer. Roughness profiles and values of Average roughness (R_a) and RMS (root mean square) roughness of the bottom layer were obtained using a Perthometer. These results were reported by Kottala et al. [42]. Interfacial radius of curvature was estimated from the roughness profiles. The results indicate that for the tablets made with same layer forces, interfacial roughness is higher for the tablets with brittle material in the first layer. This effect is due to the fragmentation of brittle powder particles creating new contact points for interlocking of the adjacent layers. Interfacial radius of curvature is lower (indicating a higher deformability of the interface due to the penetration of second layer into the first layer) for tablets with plastic material in the first layer (second layer force being constant). The reason for this mechanism can be attributed to the plasticity of the first layer, plastic materials being more deformable compared to the brittle materials. Curvature of the profiles increased with the increase of second layer force for both the plastic and brittle materials in the first layer. A large second layer force will greatly deform the particles present on the interface of first layer resulting in an interfacial boundary with low radius of curvature. Particles present at the interface will have been greatly deformed by the predominant mechanism of plastic flow and hence a large region of contact area will available for bond formation between the two adjacent layers. The higher number of junctions coupled with an increase in the roughness of the interface will result in the propagation of the crack more energetically demanding [27], and hence an increase in the interfacial SIF.

3.3.4 Effect of Interfacial Surface Roughness and Radius of Curvature on SIF

Kottala et al. [42] observed that interfacial strength of bilayer tablets is dependent on both the interfacial roughness and retained plasticity of the first layer after the application of first layer force (this effect is reflected in the form of interfacial radius of curvature, indicating the depth of penetration of second layer into the first layer). Both mechanisms will contribute to the strength of the interface. As seen in Figure 3-10, interfacial SIF of bilayer tablets made with different layer sequences increased significantly with the increase of interfacial roughness of the first layer. 'S' shaped curves indicate that SIF increased rapidly after a certain value of interfacial average roughness (R_a) and reached a plateau (remained constant) after that. This demonstrates that a critical interfacial roughness is required to have stronger interfaces that can resist the propagation of crack.

To understand the dependence of SIF on the interfacial roughness and radius of curvature, contour plots were generated as shown in Figures 3-11, 3-12, and 3-13. For avicel/avicel tablets a combination of lower interfacial radius of curvature and higher interfacial roughness of the interface produced tablets with the highest interfacial SIF. The results also indicate that for avicel/avicel tablets the interfacial radius of curvature played a key role in influencing the SIF of the interface compared to the interfacial roughness. As seen in Figure 3-11, the SIF is similar for the tablets with same interfacial radius of curvature even though there was substantial variation in their interfacial roughness.

Figure 3-12 indicates that even for avicel/lactose tablets a combination of lower interfacial radius of curvature and higher roughness of the interface produced the tablets

with greater resistance to the crack propagation. Dependency of SIF is higher on interfacial radius of curvature compared to roughness. There is a significant drop in the SIF of the tablets with the increase of interfacial radius of curvature (even though there is an increase in interfacial roughness).

As seen in Figure 3-13 for lactose/avicel tablets dependency of SIF is higher on interfacial roughness (R_a) compared to interfacial radius of curvature. SIF is higher for tablets with higher roughness even though they have interfaces with high radius of curvature. The observed differences in the dependency of SIF on the interfacial properties can be attributed to the material properties of the first layer. Due to the deformability of the plastic material in the first layer by virtue of its retained plasticity will allow the penetration of second layer into the first layer (generating interfaces with lower radius of curvature) and this mechanism will strengthen the interface (depending on the degree of its deformation). Interfacial strength obtained by this mechanism for plastic bilayer tablets is higher than the strength obtained by the mechanical interlocking of adjacent layers due to the interfacial roughness. For plastic materials there is a loss in interfacial roughness during compaction. Surface asperities present on the interface of first layer will be smoothen out by the application of a higher second layer force [42].

In case of bilayer tablets with brittle material in the first layer, the SIF is more dependent on the interfacial roughness compared to the interfacial radius of curvature. This effect can be attributed to the consolidation mechanism of brittle material, which deforms by fragmentation. As a result of brittle fracture more active sites are available for mechanical

interlocking of the adjacent layers, thus strengthening the interface. The interfacial strength obtained by this mechanism for brittle bilayer tablets is higher than the strength obtained by the deformation of the interface (layer penetration). As the particles (brittle) in the first layer are more rigid they offer greater resistance to deformation and hence a lesser degree of penetration of the second layer into the first layer (reflected in the form of higher interfacial radius of curvature).

3.4 Conclusions

The mechanical structures of bilayer tablets have become quite intricate requiring complicated tablet architectures as well as patient-friendly administration. These drug delivery systems typically require more demanding mechanical testing, characterization, and monitoring techniques during the early stages of development to optimize formulation and process conditions. In this chapter, we have developed a methodology to estimate the interfacial SIF of the bilayer tablets. SIF is a measure of materials resistance to crack propagation. Results indicated that for plastic bilayer tablets made with first layer force $\leq$ 0.5kN; SIF is higher for tablets made with lower second layer force. But this trend reverses with the increase of first layer force beyond 0.5 kN (i.e. SIF is higher for tablets made with higher second layer force). This effect can be attributed to the changes in interfacial roughness of the plastic bilayer tablets as a function of applied layer forces. In the case of brittle bilayer tablets SIF is higher for tablets made with higher second layer force (at first layer force $\leq$ 0.5kN) and this trend reverses with the increase of first layer force beyond 0.5 kN. This effect is due to the weakening of consolidated lactose particles due to over compression at higher applied forces. Layer sequence has a strong influence on the interfacial SIF of bilayer tablets. For tablets made with same second

layer force (and different layer sequence) SIF is higher for the tablets with brittle material in the first layer, and for tablets made with identical layer sequence (and different second layer force), SIF increased with the increase of second layer force.

Combination of interfacial roughness and radius of curvature have strongly influenced the ability of the interfaces to resist crack propagation. Contour plots that were generated to understand the dependency of SIF on these factors. For all the layer sequences (avicel/avicel, avicel/lactose and lactose/avicel) tablets a combination of lower interfacial radius of curvature and higher roughness of the interface has produced the tablets with highest interfacial SIF. It was also observed that for the bilayer tablets with plastic material in the first layer dependency of SIF is higher on interfacial radius of curvature compared to roughness. However, in the case of bilayer tablets with brittle material in the first layer dependency of SIF is higher on interfacial roughness compared to the interfacial radius of curvature.

3.5 Figures for Chapter 3

Figure 3-1: Different modes of crack-surface displacement: mode I (tensile mode); mode II (in-plane shear mode); mode III (antiplane shear mode).
[Source: http://en.wikipedia.org/wiki/Fracture_mechanics**].**

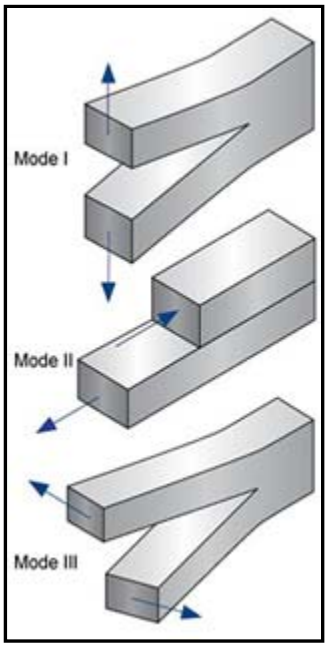


Figure 3-2: Schematic of a bilayer tablet with interfacial crack.

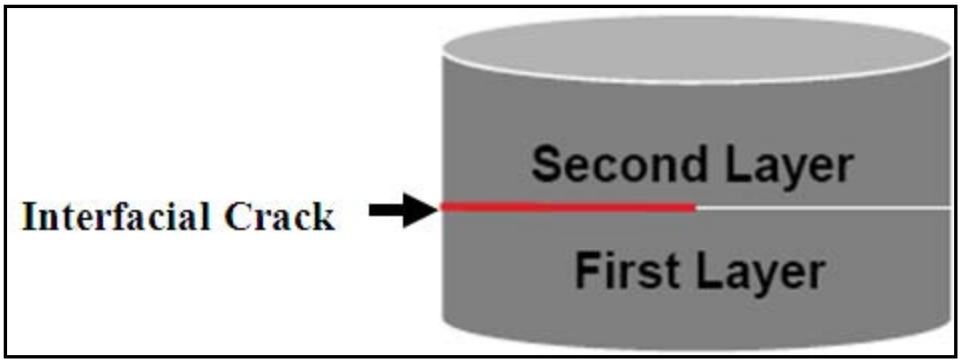


Figure 3-3: Schematic of a bilayer tablet connected to the load cell of the axial tester.

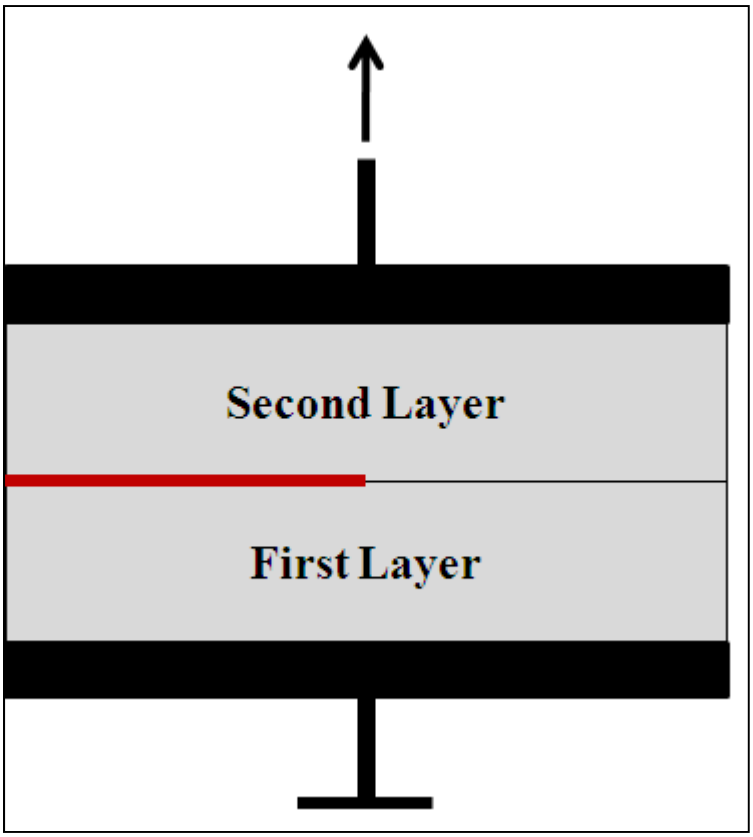


Figure 3-4: Interfacial crack characterization.
[Source: J. Toribo et al. Engineering Failure Analysis 16 (2009)]

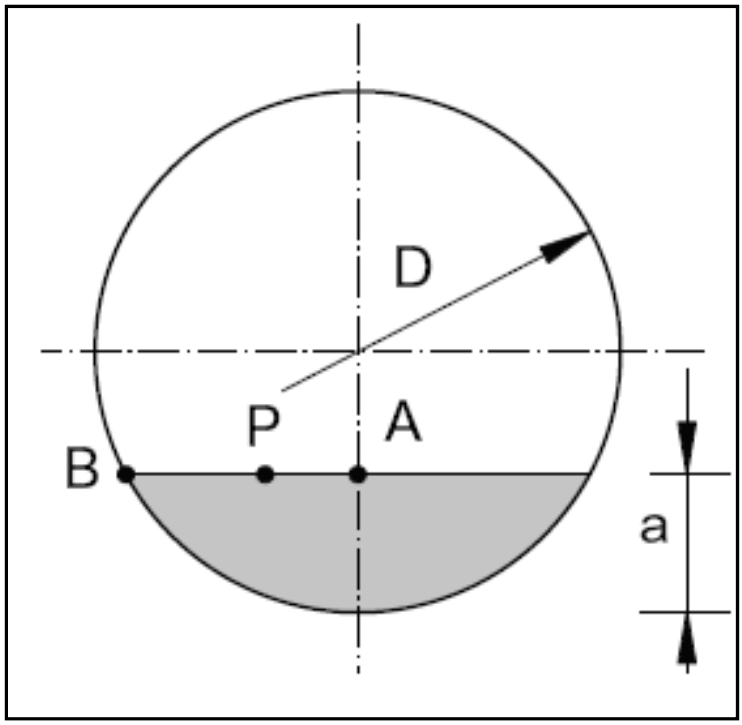


Figure 3-5: Effect of layer forces on the interfacial stress intensity factor of tablets made of plastic (avicel/avicel) material.

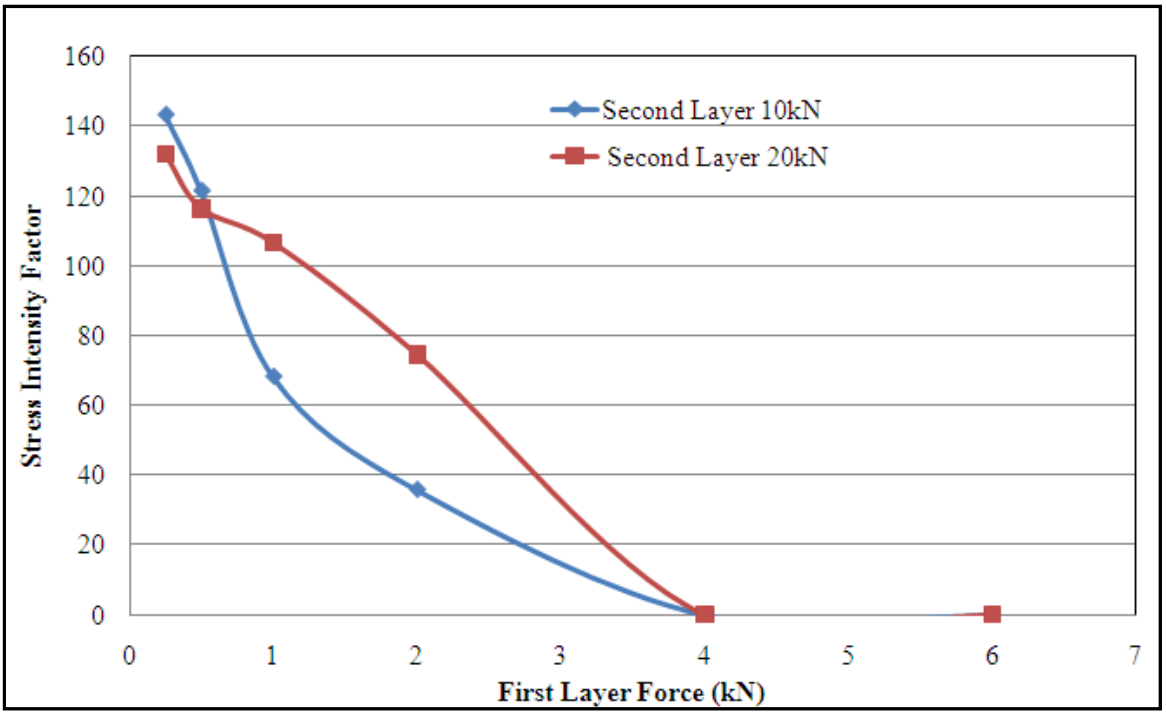


Figure 3-6: Effect of layer forces on the interfacial stress intensity factor of tablets made of brittle (lactose/ lactose) material.

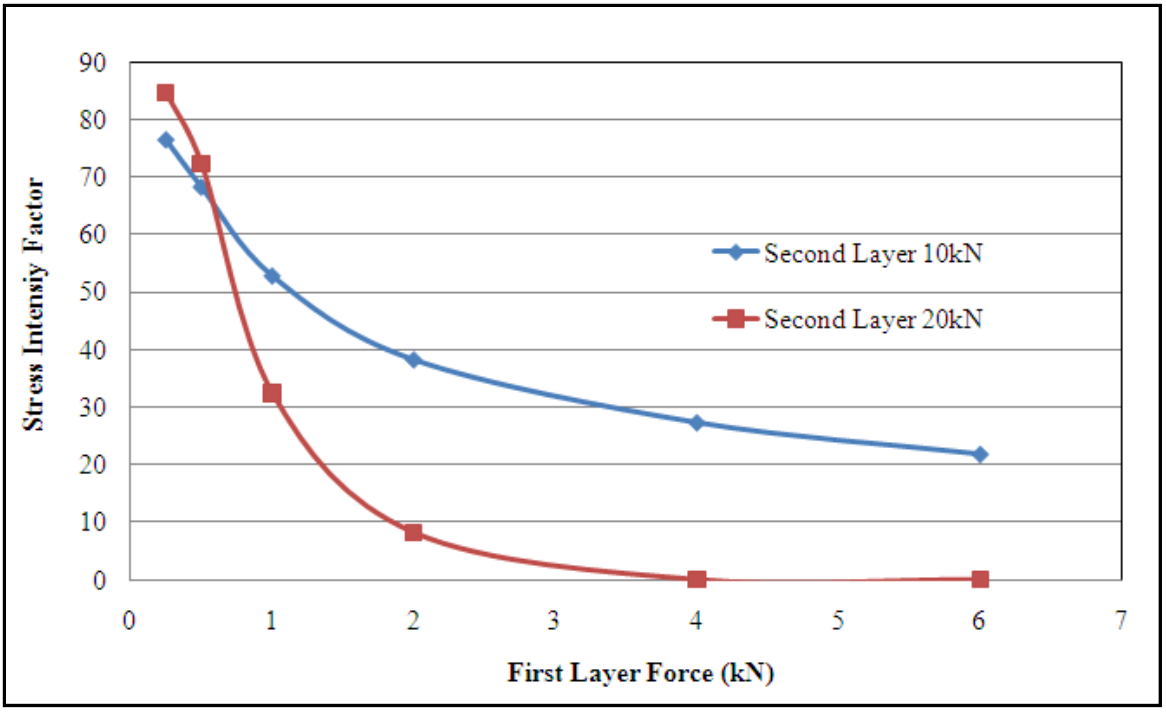


Figure 3-7: Effect of first layer force and material properties on the interfacial stress intensity factor of bilayer tablets (Second Layer Force: 10 kN).

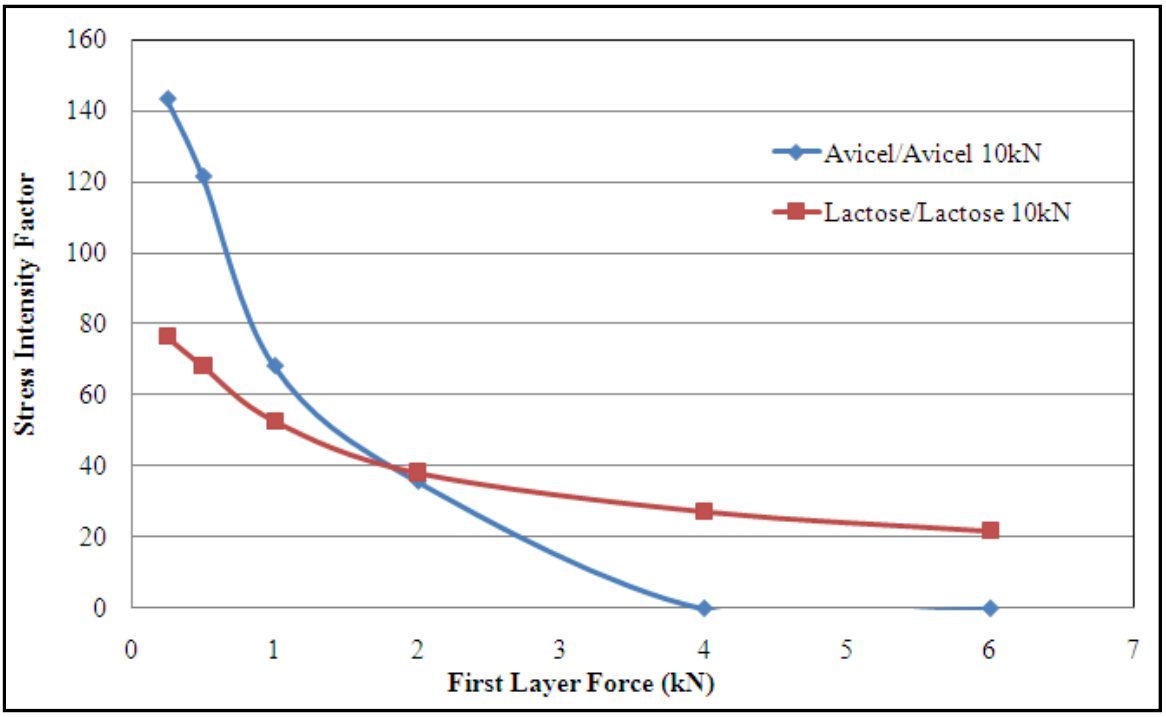


Figure 3-8: Effect of first layer force and material properties on the interfacial stress intensity factor of bilayer tablets (Second Layer Force: 20 kN).

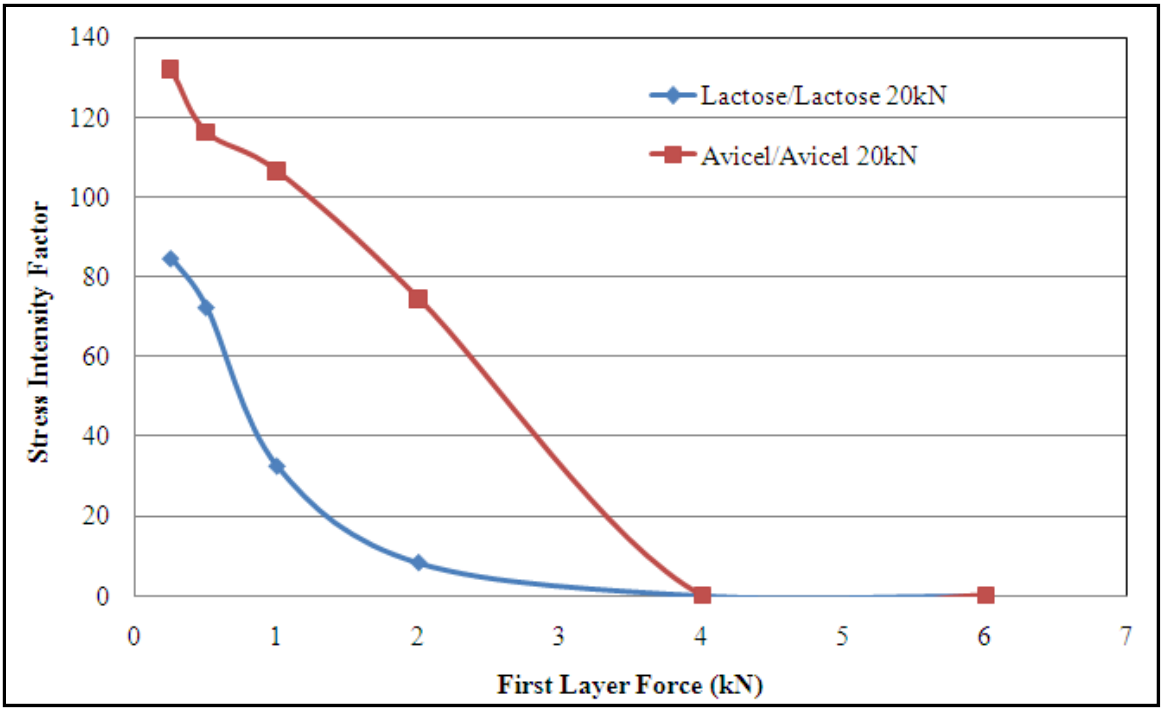


Figure 3-9: Effect of layer sequence and layer forces on the interfacial stress intensity factor of bilayer tablets.

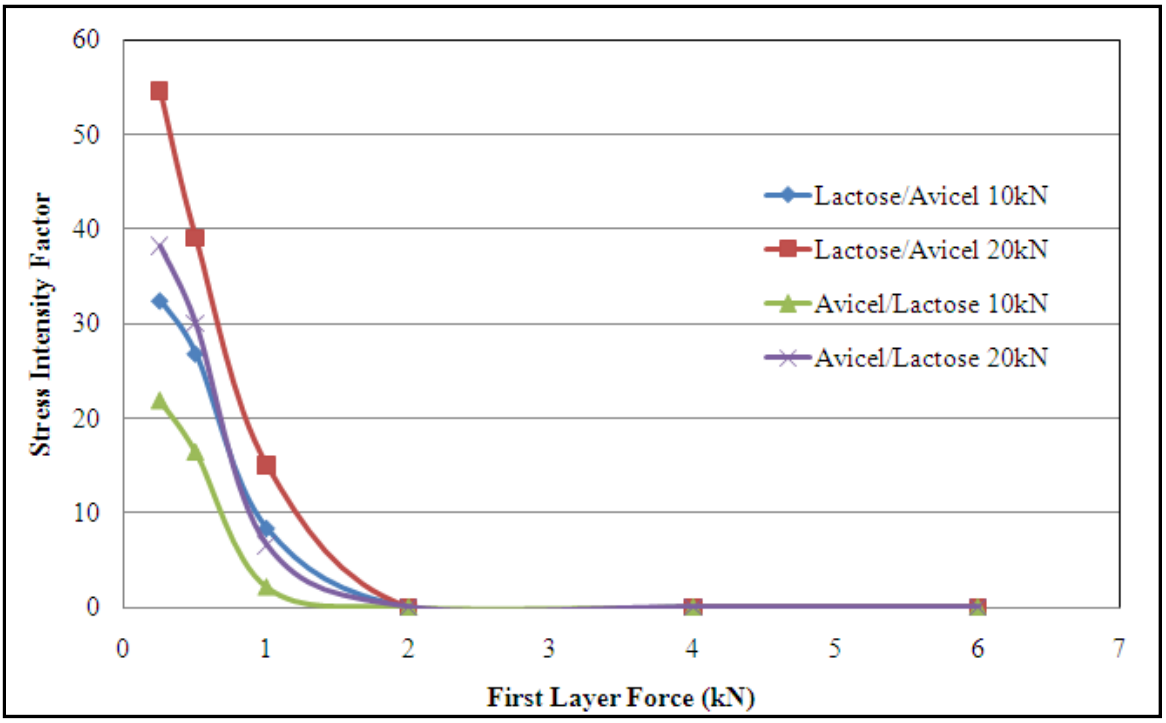


Figure 3-10: Effect of interfacial roughness on the stress intensity factor of bilayer tablets.

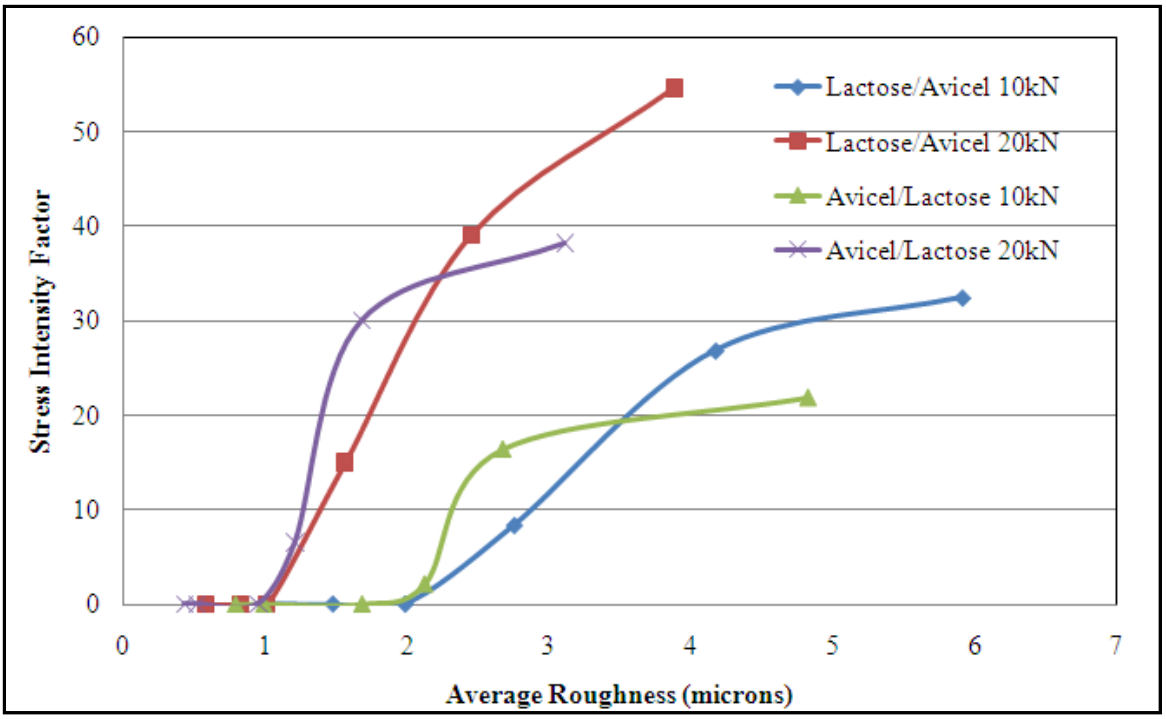


Figure 3-11: Contour plot for influence of interfacial radius of curvature and roughness on the SIF (of avicel/avicel bilayer tablets).

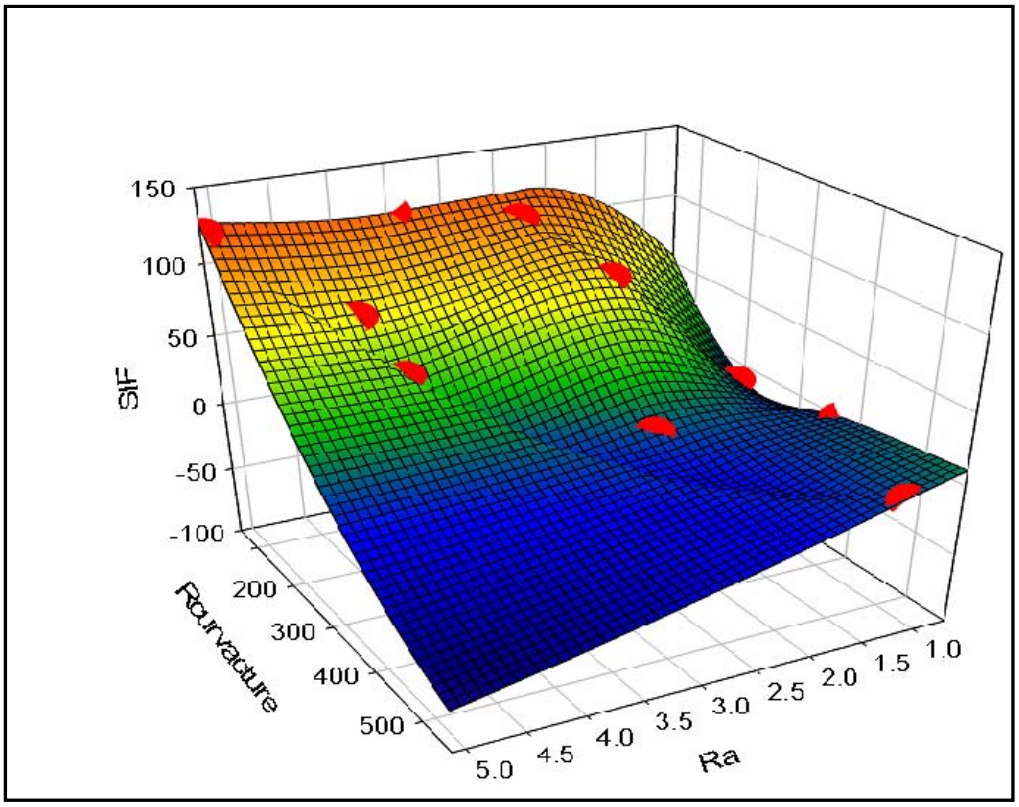


Figure 3-12: Contour plot for influence of interfacial radius of curvature and roughness on the SIF (of avicel/lactose bilayer tablets).

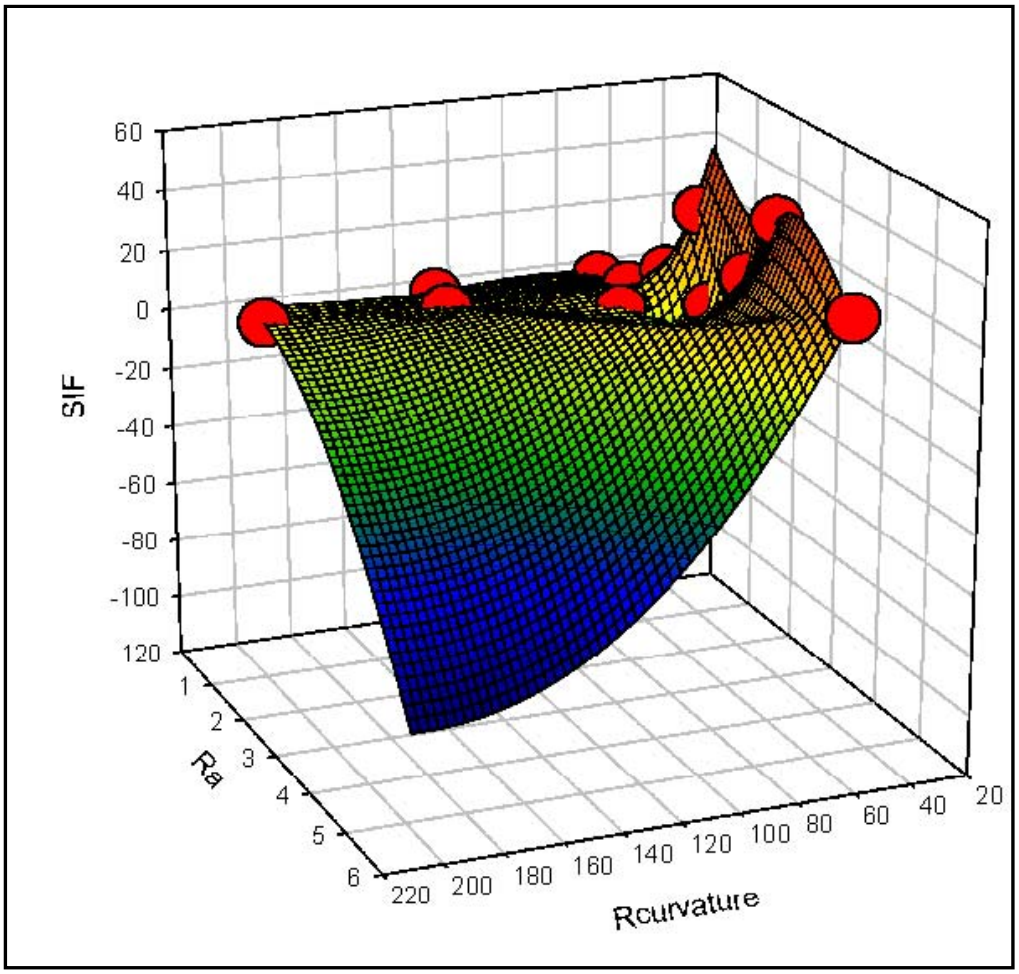
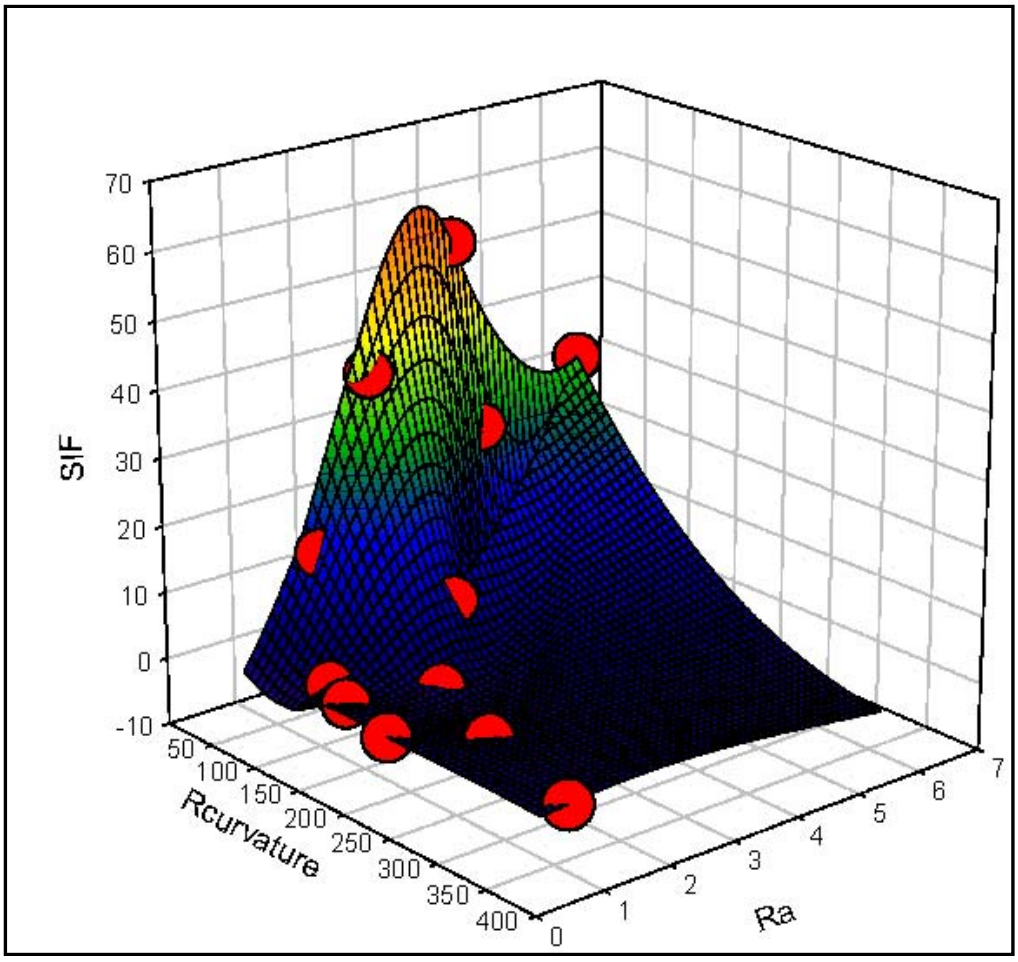


Figure 3-13: Contour plot for influence of interfacial radius of curvature and roughness on the SIF (of lactose/avicel bilayer tablets).



Chapter 4: Impact of Bilayer Compression Process Parameters and Material Properties on the Mechanical Strength of Bilayer Tablets

4.1 Background

Tensile strength is the key quality attribute of the bilayer tablets. It is critical to maintain the structural integrity of bilayer tablets during their production and during the down-stream operations like tablet coating and packaging. Material properties of the individual layers and bilayer compression process parameters have a strong influence on the tensile strength of the tablets. Dietrich et al. [23] 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 [43] 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 chapter 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 chapter 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.

4.2 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.

4.2.1 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. [10] 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 [44] reported the Young's modulus of avicel and lactose as 13.2 and 53GPa 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.

4.2.2 First Layer Force: Studies carried out by Akseli et al. [25] 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 [45]. 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 [45]. (Levels Studied: low: 2kN, center point: 3kN, high: 4kN)

4.2.3 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 [46]. This may result in capping or delamination of the tablet along the interface during manufacturing or immediately after manufacturing [8]. (Levels Studied: low: 14kN, center point: 18kN, high: 22kN)

4.2.4 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 [47]. 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)

4.2.5 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)

4.2.6 Lubricant Level: Magnesium sterate 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 [48]. 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. [23] 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. [47] 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.)

4.3 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 2 levels (High, 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 2 replicates run of the four layer sequences (avicel/avicel, lactose/lactose, avicel/lactose, and lactose/avicel) by layer (1st, 2nd) combinations. At each of these four combinations, 2 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). Detailed DOE plan is presented in the appendix A.

4.4 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 Sterate (Tyco Mallinckrodt, St. Louis, MO) was used as lubricant.

4.4.1 Bilayer Tablets Preparation and Testing

Blends for the bilayer compression are binary mixtures of an excipient and magnesium sterate. Excipients are mixed with 0.25, 0.50, and 0.75% w/w magnesium sterate in a 22L bin blender for 60 revolutions (3 minutes 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).

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 (Figure 4-1) using a cyanoacrylate based glue (LOCTITE®,

Henkel Corporation, Avon, OH) and left for an hour to ensure a good adhesion [25]. 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 [25]. 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 with-in the bilayer compact upon axially loading the system.

4.5 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 7 main effects and 21 2-way interactions. Table 4-1 shows the p-values associated with each term in the 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, layer 1 and layer 2 by compaction speed 2-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 2-way interaction and main effects that were not part of a 2-way interaction are discussed in the following sections.

4.5.1 Effect of Materials on the Strength of Bi-layer Compacts

Figure 4-2 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 [44] reported the Young's modulus of avicel and lactose as 13.2 and 53GPa 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 [49]. 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 [49]. The surface roughness of avicel in the first layer was reduced significantly (at the first layer forces: 2, 3 and 4kN) thus resulting in a decrease in inter-particulate attraction and mechanical interlocking between the two adjacent layers.

4.5.2 Effect of First Layer Material and Compaction Speed

Figure 4-3 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 [47].

4.5.3 Effect of Second Layer Material and Compaction Speed

Figure 4-4 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.

4.5.4 Effect of First Layer Material and Second Layer Compaction Force

As indicated in Figure 4-5, 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 [25]. 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 [25].

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 [25]. This will reduce the mechanical interlocking of the adjacent layers and hence their bonding strength.

4.5.5 Effect of Compaction Speed and Lubricant Concentration

As shown in Figure 4-6, 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 [48]. 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 [23].

4.6 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.

4.7 Figures for Chapter 4

Figure 4-1: A close-up photograph of the bilayer tablet to be tested.

Figure 4-2: Effect of Materials on the strength of bilayer tablets (Ex1= Material in layer 1; Ex2= Material in layer 2)

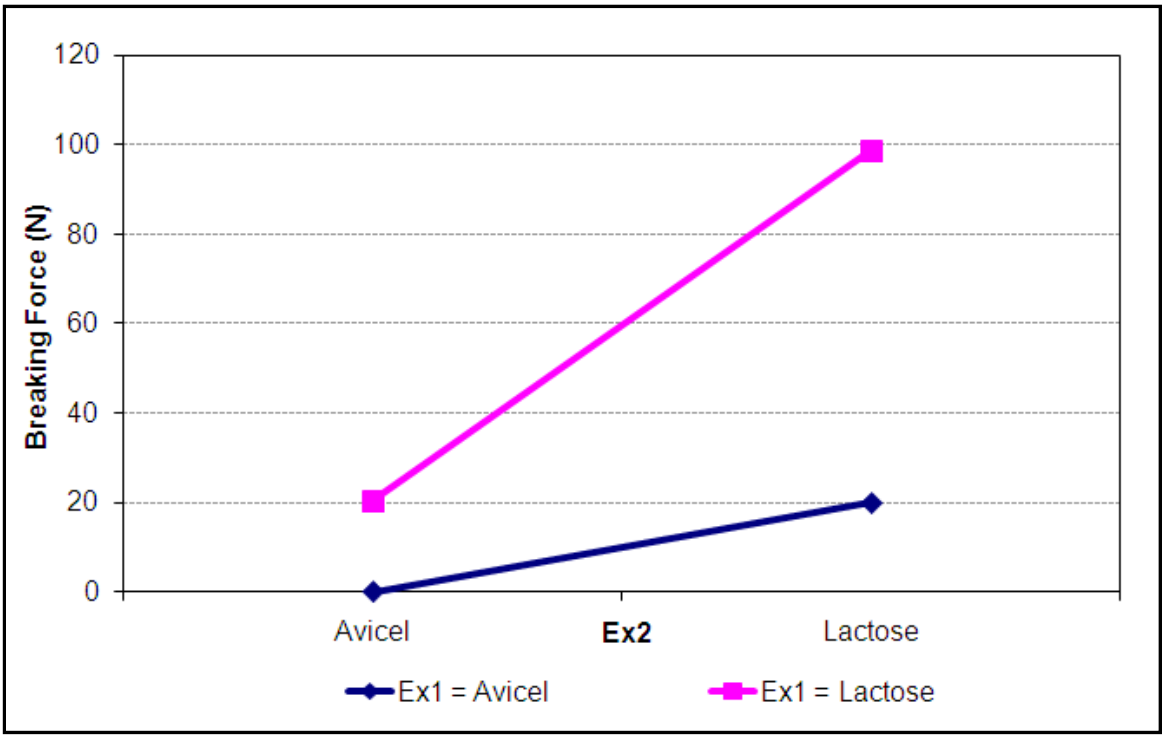


Figure 4-3: Effect of first layer material and compaction speed on the strength of bilayer tablets (Ex1= Material in layer 1)

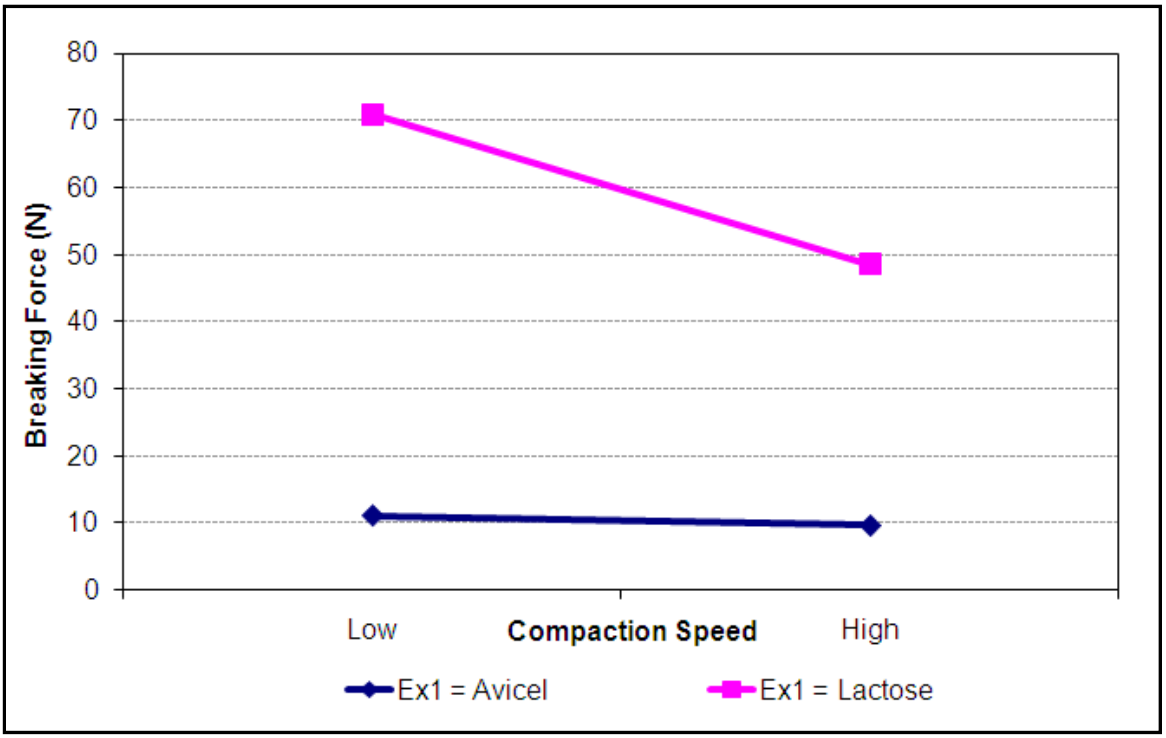


Figure 4-4: Effect of second layer material and compaction speed on the strength of bilayer tablets (Ex2= Material in layer 2)

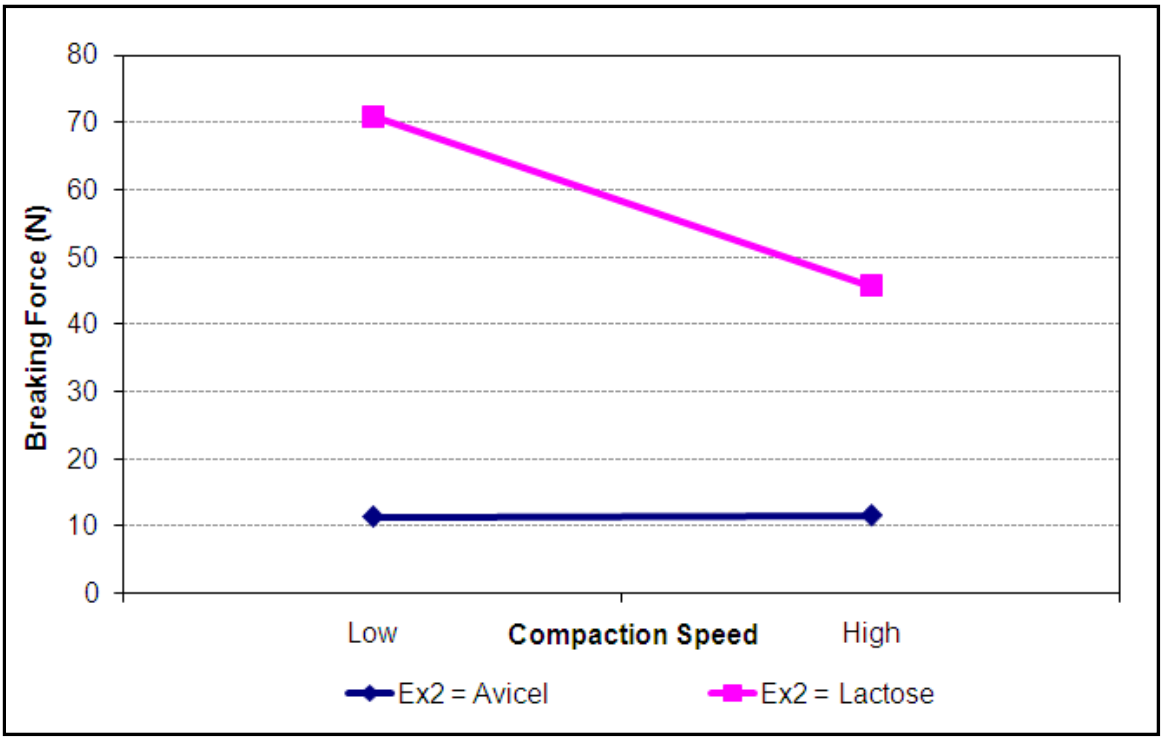


Figure 4-5: Effect of first layer material and second layer force on the strength of bilayer tablets (Ex1= Material in layer 1)

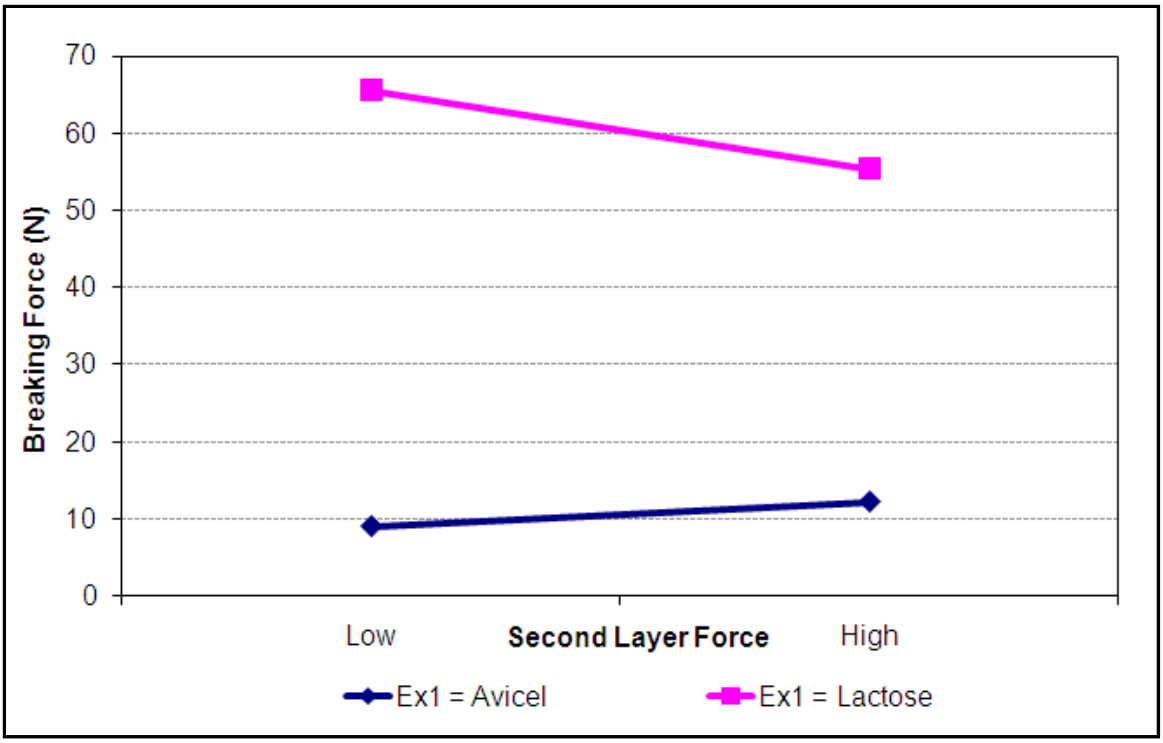
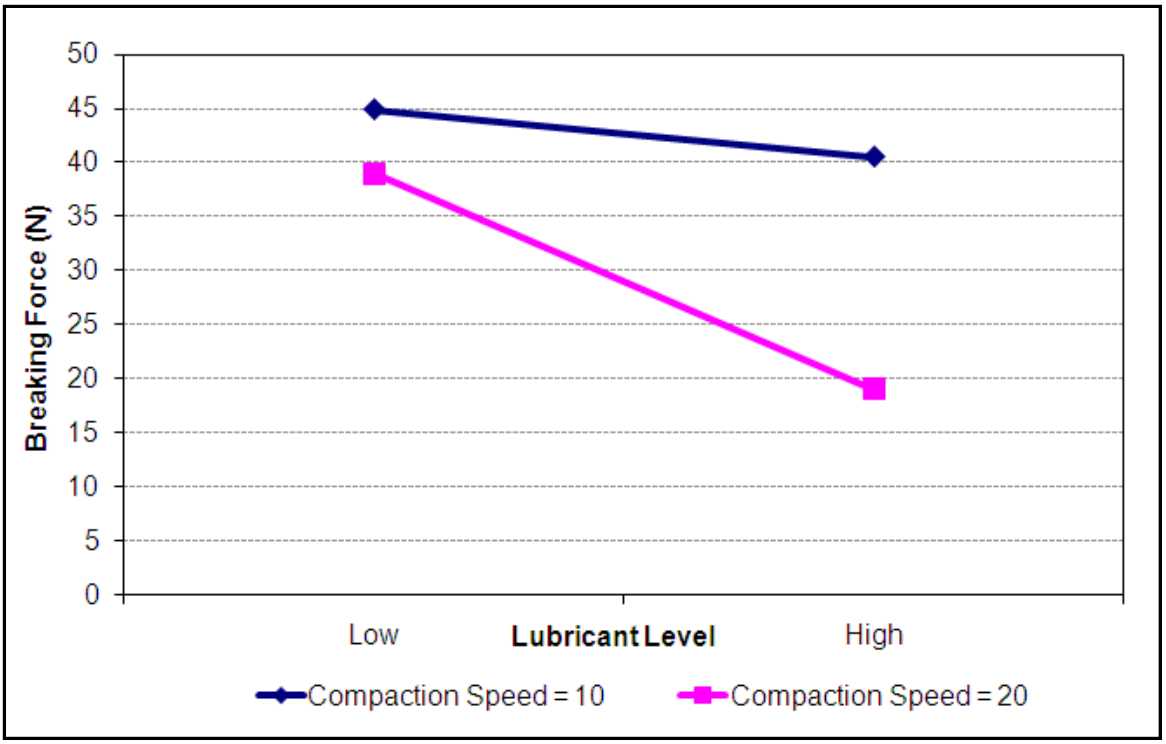


Figure 4-6: Effect of compaction speed and lubricant level on the strength of bilayer tablets



4.8 Tables for Chapter 4

Table 4-1: p-values of the different interactions.

Effect	P-Value
†Layer 1 Excipient (EX1)	<0.0001
Layer 1 Compression Force (CF1)	0.0694
†Layer 2 Excipient (EX2)	<0.0001
Layer 2 Compression Force (CF2)	0.4923
Excipient Ratio (EXRatio)	0.4736
†Compaction Speed (CS)	0.0024
†Magnesium Stearate Level (MagSt)	0.0045
EX1*CF1	0.2108
†EX1*EX2	<0.0001
EX1*CF2	0.0694
EX1*EXRatio	0.3172
†EX1*CS	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	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

† Significant Interaction

Chapter 5: Impact of Environmental Conditions on the Strength of Bilayer Tablets

5.1 Background

As with conventional single layer tablets, physical stability of bilayer tablets during storage is a key factor for consideration during product development as this may impact the tensile strength, friability, disintegration, dissolution and other performance characteristics. Humidity and temperature along with storage time are reported to play a crucial role in determining the mechanical characteristics of bilayer tablets. Affinity for water adsorption changes with material properties. This difference in the material-water interaction might lead to the differences in the radial expansion of the individual layers in a bilayer tablet. Radial stresses will be generated due to the uneven expansion of individual layers, resulting in their separation at the interface.

A number of cases were reported in the literature regarding the effect of moisture sorption on the strength of single layer tablets. Studies were carried out by Nakabayashi et al. [50] to understand the effect of moisture on physical stability. These studies have concluded that the effect of moisture sorption on tablet strength is dependent on the characteristics of the formulation. Nystrom and Karehill [51] reported that upon storage, surface area for sodium chloride remained almost constant but the tablet strength increased by two fold in short time. Bolhuis et al. [52] observed that upon storage at higher humidity, tablet strength and BET- specific surface area of tablets made with sucrose granulations decreased significantly due to moisture sorption. Subsequent storage of the tablets in a dry atmosphere resulted in an increase in strength but no change in BET- specific surface area. The irreversible decrease in specific surface area of the

tablets on exposure to humid conditions is due to the blocking of the very narrow pores in the tablets by sorbed moisture. Lerk [53] has demonstrated that amorphous lactose absorbs up to 9% water and it crystallizes under the loss of water. This crystallization leads to the formation of solid bridges between the particles and hence the increase in tablet strength. Down et al. [54] observed that rearrangement of solid material can occur at the particle surfaces within the tablet. This rearrangement can lead to the formation of solid bridges between particles. Adsorbed water can facilitate the rearrangement of solid material within the tablet matrix. This mechanism explains the post compaction increase in tensile strength of tablets containing water soluble materials like sodium chloride and saccharose.

In the literature several mechanisms have been proposed to explain the post compaction strength changes of non-hygroscopic pharmaceutical materials. For these materials post compaction strength increase is due to either formation of solid bridges between the particles or due to an increase in the bonding surface area of intermolecular attraction forces. El Gindy et al. [55] have shown that post compaction deformation of particles occurs in the tablet and this mechanism is described as stress relaxation. This continuing particle deformation will lead to decreased interparticulate distance and to an increased surface area for interparticulate attractions. Hall et al. [56] observed that mobility of water within the tablet can cause crystallization of dissolved material. Dissolution of solid material is made possible due to the condensation of adsorbed water at particle surfaces. The crystallization of dissolved material can lead to the formation of solid bridges between the particles. Several studies have also indicated that ambient humidity

during tablet storage has substantial impact on the tensile strength of tablets. This effect varies for different materials and storage time. The reason for this is due to the difference in the rate of change in the mechanical strength between tablets of the respective material. Thus, to further understand the post compaction changes in the tablet strength due to adsorption of moisture, it is of interest to study the relationship between the mechanical strength and the post compaction storage time of the tablets.

Although such relationships have been presented in the literature for single layer tablets they have not been reported for bilayer tablets. There is a dearth of knowledge on understanding the impact of storage conditions on the mechanical strength of bilayer tablets manufactured with different materials at various processing conditions. Most of the work in the literature dealt with the effect of moisture. Very few papers considered effects of temperature along with humidity on the tensile strength of single layer tablets. Tablets evaluated in these studies were manufactured at lab scale, and only the impact of material properties on the tablet strength upon storage was evaluated. This chapter thoroughly evaluates the impact of manufacturing process parameters on the performance characteristics of bilayer tablets that were stored at accelerated humidity and temperature conditions immediately after their compression.

5.2 Statistical Design of Experiments (DOE)

A full $3x2^4$ factorial design was used to evaluate the effects of storage condition, first and second layer excipient combination, dwell time, lubricant level, and first layer compression force on breaking force. The second layer compression force was fixed at 18

kN. Tablets were tested from each storage condition at 1, 3, and 7 days. The levels for each factor are described below:

- Storage condition: 2 Levels (40C/45%RH, 40C/75%RH)
- First and second layer excipient combinations: 3 Levels (lactose/avicel, lactose/lactose, avicel/lactose)
- Compaction speed: 2 Levels (10 rpm, 20 rpm)
- Lubricant (Mg.st.) concentration: 2 Levels (0.25%, 0.75%)
- First Layer compression force: 2 Levels (2 kN, 4 kN)

5.3 Materials and Methods

The materials and methods used to prepare and test the bilayer tablets have been described in Chapter 4.

5.4 Results and Discussion

Effects of the six factors (storage condition, first and second layer excipient combination, dwell time, magnesium stearate level, first layer compression force, and time) on breaking force of the bilayer tablets was evaluated using PROC GLM of SAS (SAS Institute Inc, Cary, North Carolina). A model was fit that contained the six main effects, 15 2-way interactions and 20 3-way interactions. Table 5-1 shows the p-values associated with each term in the model. Any term with a p-value less than 0.05 was considered significant.

The significant terms are Day, Condition, Combination, MagSt, Day*Cond, Day*Comb, Day by CF1, Comb*DT, Comb*MgSt, DT*CF1, Day*Cond*Comb, Day*Comb*MgSt, Day*Comb*CF1, Day*DT*CF1, Condition*Comb*CF1, Comb*DT*CF1. To visualize

factor effects, only significant terms that are not part of a higher order term are ploted and discussed in the following sections. This includes the Day*Cond*Comb, Day*Comb*MgSt, Day*Comb*CF1, Day*DT*CF1, Condition*Comb*CF1, Comb*DT*CF1 three way interactions.

5.4.1 Effect of Storage Conditions and Time on the Strength of Bi-layer Tablets

For avicel-lactose (Figure 5-1) and lactose-avicel (Figure 5-2) tablets, increasing humidity lowers tablet strength with a similar difference at days 1 and 3. The effect is greater for lactose-avicel at day 7. There is a general downward trend in tablet strength over time. This effect can be attributed to the formation of multilayers of water at the particle surfaces. Such layers may then disturb or reduce intermolecular attraction forces and thereby reduce the tablet strength [57].

For lactose-lactose (Figure 5-3) tablets, there is a significant interaction between time and humidity level. Increasing humidity increases tablet strength at days 1 and 3 but reduces tablet strength at day 7. There is an upward trend at both humidity conditions from day 1 to day 7. The lower humidity condition continues to increase until day 7 whereas there is a significant negative trend for the higher humidity condition. The increase in tensile strength of lactose-lactose tablets with an increase of humidity and storage time from day 1 to day 3 is due to the crystallization of amorphous lactose particles at contact points between the particles, which results in the formation of strong solid bridges. A possible mechanism for the decrease of tablet strength at the higher humidity condition from day 3 to day 7 is the dissolution of solid material (amorphous lactose particles) because of the

condensation of adsorbed water at particle surfaces. This phenomenon weakens the contact points between the particles and decreases the tablet strength.

5.4.2 Effect of First Layer Force and Storage Condition on the Strength of Bi-layer Tablets

For all three material combinations (Figures 5-4, 5-5, and 5-6), strength of the bilayer tablets decreased with the increase of humidity. The effect of first layer force shows a slight interaction with storage condition for avicel-lactose (Figure 5-4) and lactose-avicel (Figure 5-5) bilayer tablets, but the dependence of the storage condition effect on the first layer force is small.

For lactose-lactose (Figure 5-6) tablets, the effect of first layer force shows a strong interaction with storage condition. The dependence of the storage condition effect on the first layer force is also greater for lactose-lactose tablets. At the lower humidity condition, tablet strength is independent of first layer force but at the higher humidity condition tablets made with higher first layer force are stronger than the ones made with lower first layer force. The reason for this effect might be due to the consolidation mechanism of the brittle materials (which consolidate by fragmentation). By increasing first layer compression force, due to brittle fracture of lactose particles, new surfaces are generated at the interface of the first layer, resulting in the formation of more solid bridges between the particles at the increased humidity. Hence, tablets made with higher first layer compression force showed an increase in tablet strength upon storage at the higher humidity condition.

5.4.3 Effect of First Layer Force and Compaction Speed on the Strength of Bi-layer Tablets

As shown in Figures 5-7 and 5-8, for avicel-lactose and lactose-avicel tablets that were stored in the accelerated ambient conditions (higher humidity and temperature), increasing compaction speed decreases the tablet strength, as the reduction in dwell time (due to increased compaction speed) results in the weaker consolidation of powder particles. Increasing the first layer force has in general increased the tablet strength slightly. This may be due to the generation of new surfaces at the first layer interface and eventual recrystallization of these solid contacts upon storage. Recrystallization of the amorphous particles present on the interface will result in the formation of strong solid bridges.

For lactose-lactose tablets (Figure 5-9), the compaction speed effect strongly depends on the first layer force. At low first layer compression force, low compaction speed provides the highest tablet strength. But at the high first layer compression force, high compaction speed provides the highest tablet strength. This effect can be attributed to the generation of new surfaces due to the fragmentation of lactose particles. At low first layer force, higher dwell time is required for the generation of new surfaces through particle fracture. Particle fracture will result in the formation of strong solid bridges with the increase of first layer force. It is interesting to note that stronger tablets were formed at higher compaction speed (lower dwell times). According to Tye et al. [47], higher compaction speed results in more extensive fragmentation of brittle materials. Consequently, a larger number of clean bonding sites may be available for bonding. Upon storage the

amorphous particles at the bonding sites will recrystallize resulting in the increase of tablet strength.

5.4.4 Effect of First Layer Force and Storage Time on the Strength of Bi-layer Tablets

For avicel-lactose tablets (Figure 5-10) first layer compression force has no significant impact on the strength of the tablets. Upon storage at elevated humidity conditions, strength of the tablets decreased with storage time. This effect is due to the weakening of the contact points between the powder particles due to moisture adsorption on the particle surfaces.

As shown in Figure 5-11, strength of lactose-avicel tablets showed a strong interaction with first layer compression force upon storage. Bilayer tablets made with higher first layer force are stronger than those made with lower first layer compression force. The effect of first layer compression force is greater at day 3 and 7 than at day 1. This phenomenon can be attributed to the generation of new surfaces at the interface due to the fragmentation of lactose particles (in the first layer) upon the increase of first layer force. Amorphous lactose particles present in the newly fractured surfaces will recrystallize upon storage and will lead to the formation of strong solid bridges between the adjacent layers.

As shown in Figure 5-12, for lactose-lactose tablets first layer compression force has no significant impact on the strength of bilayer tablets. The strength of the tablets increased from day 1 to day 3 upon storage at and remained constant till day 7. The increase in

tablet strength upon storage can be attributed to the recrystallization of amorphous lactose and formation of strong solid bridges.

5.4.5 Effect of Magnesium Sterate and Storage Time on Strength of Bilayer Tablets

Tablet strength decreased with the increase of magnesium sterate content for all three material combinations. Tablet strength of the avicel-lactose (Figure 5-13) & lactose-avicel (Figure 5-14) tablets decreased with storage time. It was widely referenced in the literature that increased lubricity will result in the reduction of tablet strength due to reduced friction between powder particles.

Lactose-lactose (Figure 5-15) tablets show an increasing trend in the strength from day 1 to day 3 with little change from day 3 to day 7. The reason for this anomaly is the formation of solid bridges at the contact points between the particles of the tablets upon storage at accelerated temperature and humidity conditions.

5.4.6 Effect of First Layer Force and Storage Time on Strength of Bilayer Tablets

Strength of the tablets increases from Day 1 to Day 3 and levels off from Day 3 to Day 7 for both compaction speeds (Figures 5-16 and 5-17). There is no effect of first layer compression force on day 1 for either compaction speeds. At day 3, tablet strength increases with higher first layer compression force for the high compaction speed (Figure 5-17) but there is no difference at the low compaction speed (Figure 5-16). From day 3 to day 7, the tablet strength decreases slightly for the high first layer compression force but remains flat for the low first layer compression force.

5.5 Conclusions

Bilayer tablets offer specific advantages and capabilities which are not achievable by single layer tablets, but bilayer tablet design also offers a new set of challenges. Apart from the formulation design and manufacturing process considerations, physical stability of bilayer tablets during storage is a key factor for consideration during product development as this may impact the quality attributes of the bilayer tablets such as tensile strength, layer adhesion, friability, disintegration, and dissolution. The work discussed in this chapter enhances the understanding of the impact of bilayer manufacturing process parameters and storage conditions and the effects of their interactions on the performance of bilayer tablets.

As expected, storage conditions and storage time have significant impact on the strength of bilayer tablets. For avicel-lactose and lactose-avicel tablets, tablet strength decreased with the increasing humidity and storage time. But, for lactose-lactose tablets due to the formation of solid bridges upon storage, an increase in tablet strength was observed. The effect of first layer compression force shows a strong interaction with storage condition for lactose-lactose tablets. However, for avicel-lactose and lactose-avicel tablets, effect of first layer compression force shows a slight interaction with storage condition. Compaction speed is independent of the first layer force for avicel-lactose and lactose-avicel tablets. For these tablets, a decrease in tablet strength with an increase of compaction speed was observed. There is a strong interaction between the first layer compression force and compaction speed for the lactose-lactose tablets.

5.6 Figures for Chapter 5

Figure 5-1: Effect of storage condition and storage time on the strength of avicel-lactose bilayer tablets.

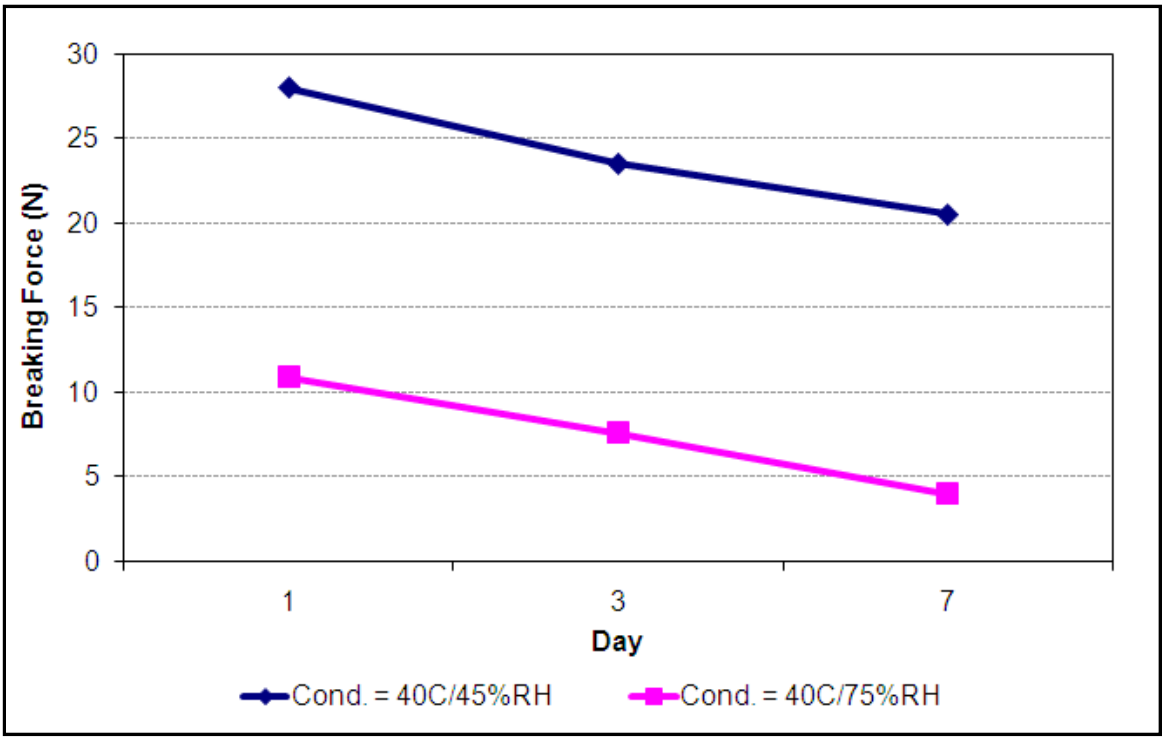


Figure 5-2: Effect of storage condition and storage time on the strength of lactose-avicel bilayer tablets.

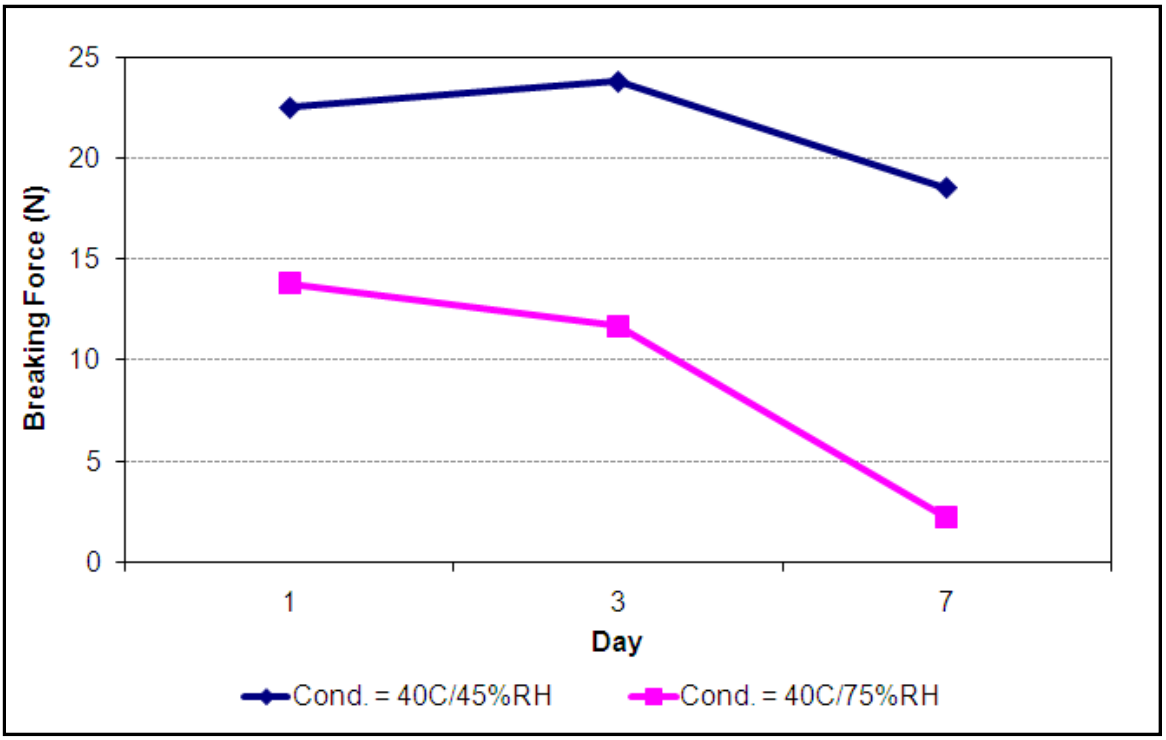


Figure 5-3: Effect of storage condition and storage time on the strength of Lactose-Lactose bilayer tablets.

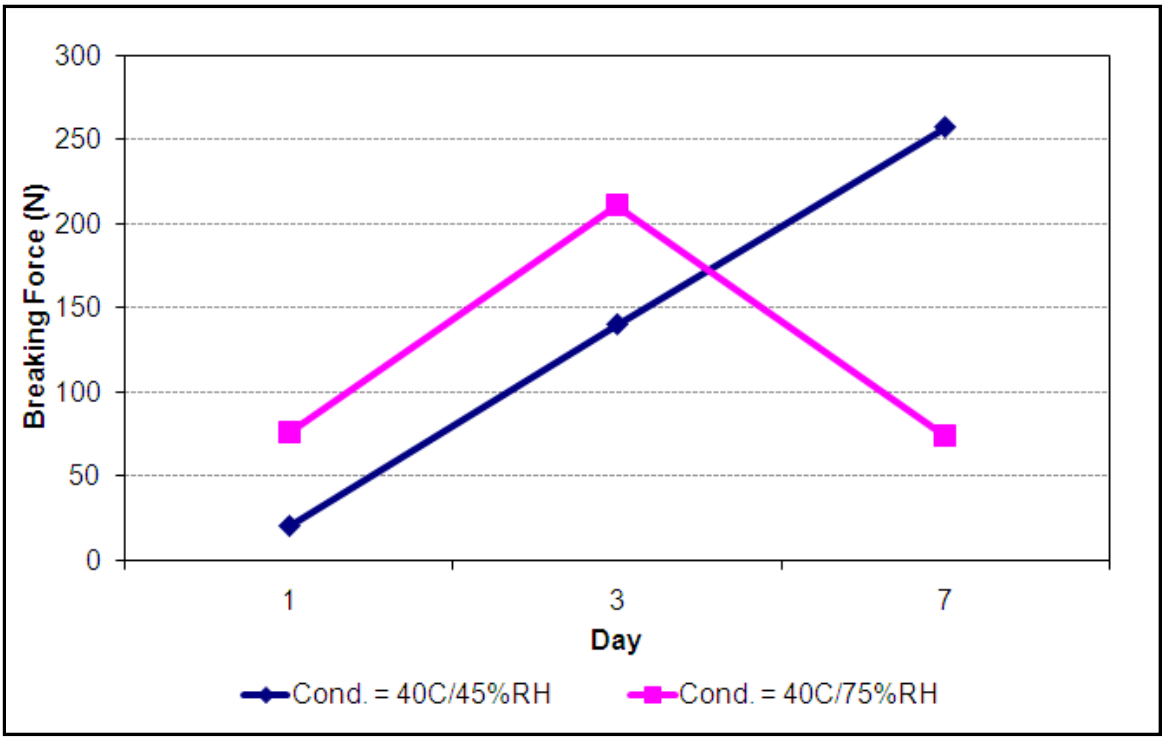


Figure 5-4: Effect of first layer force and storage condition on the strength of avicel-lactose bilayer tablets

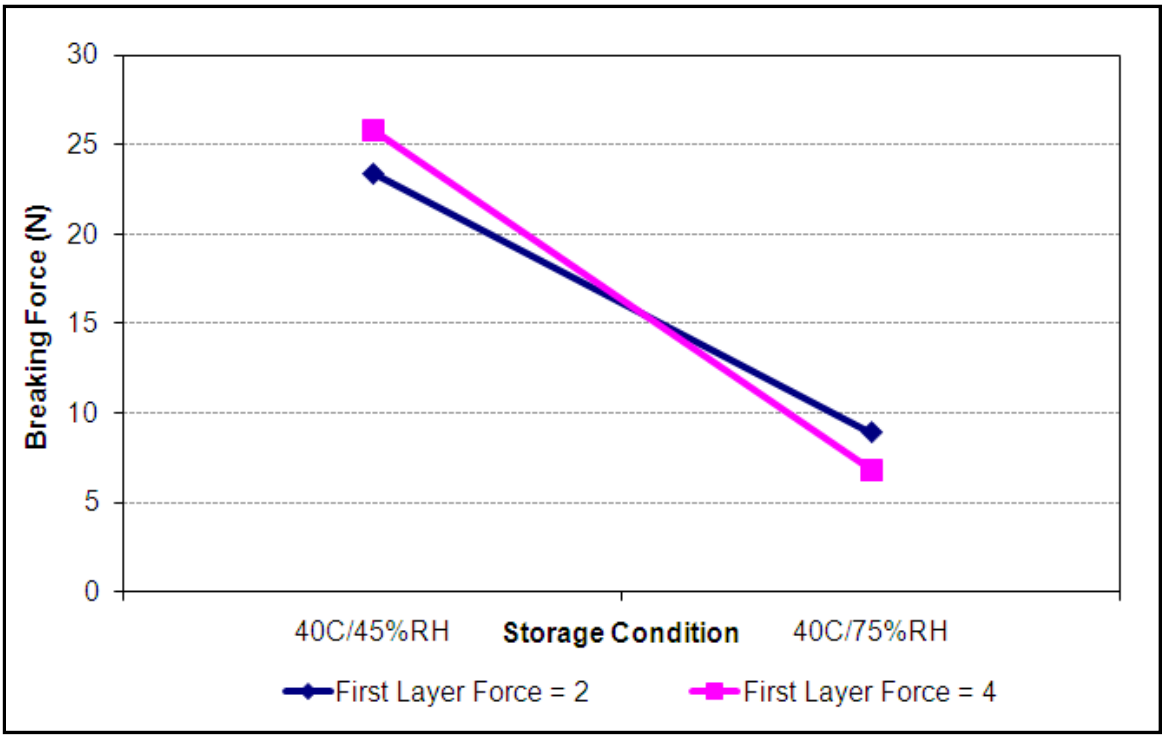


Figure 5-5: Effect of first layer force and storage condition on the strength of lactose-avicel bilayer tablets

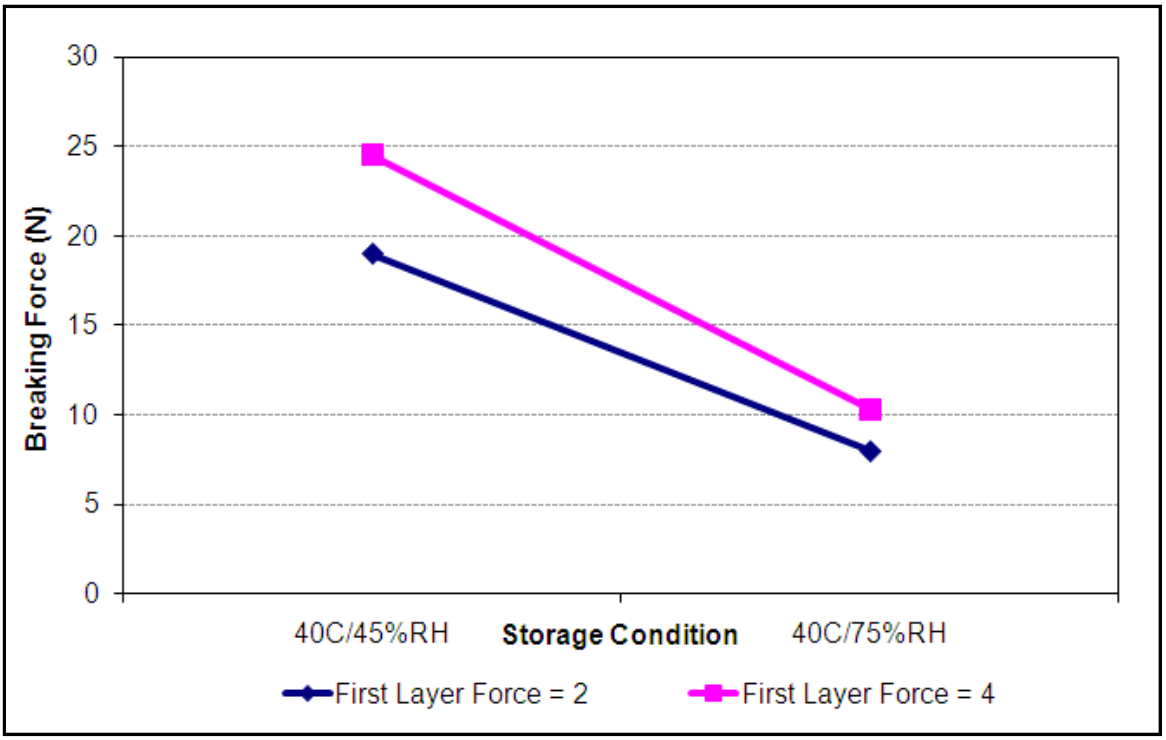


Figure 5-6: Effect of first layer force and storage condition on the strength of Lactose-Lactose bilayer tablets

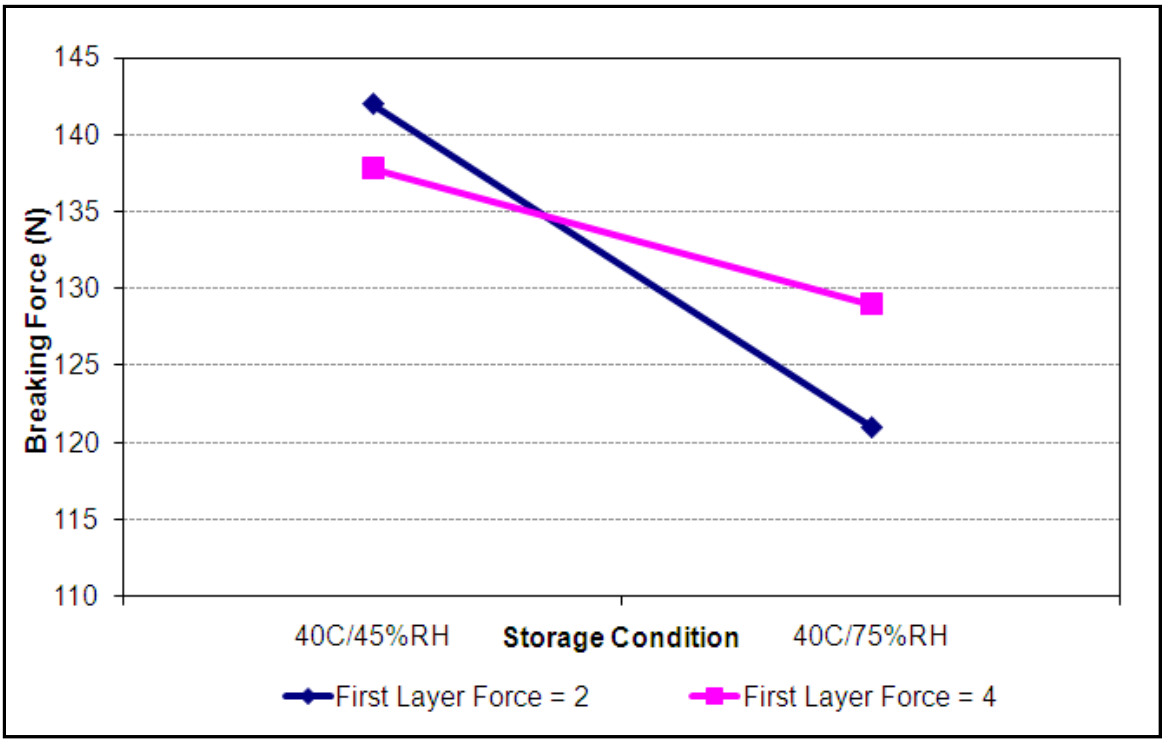


Figure 5-7: Effect of first layer force and compaction speed on the strength of avicel-lactose bilayer tablets

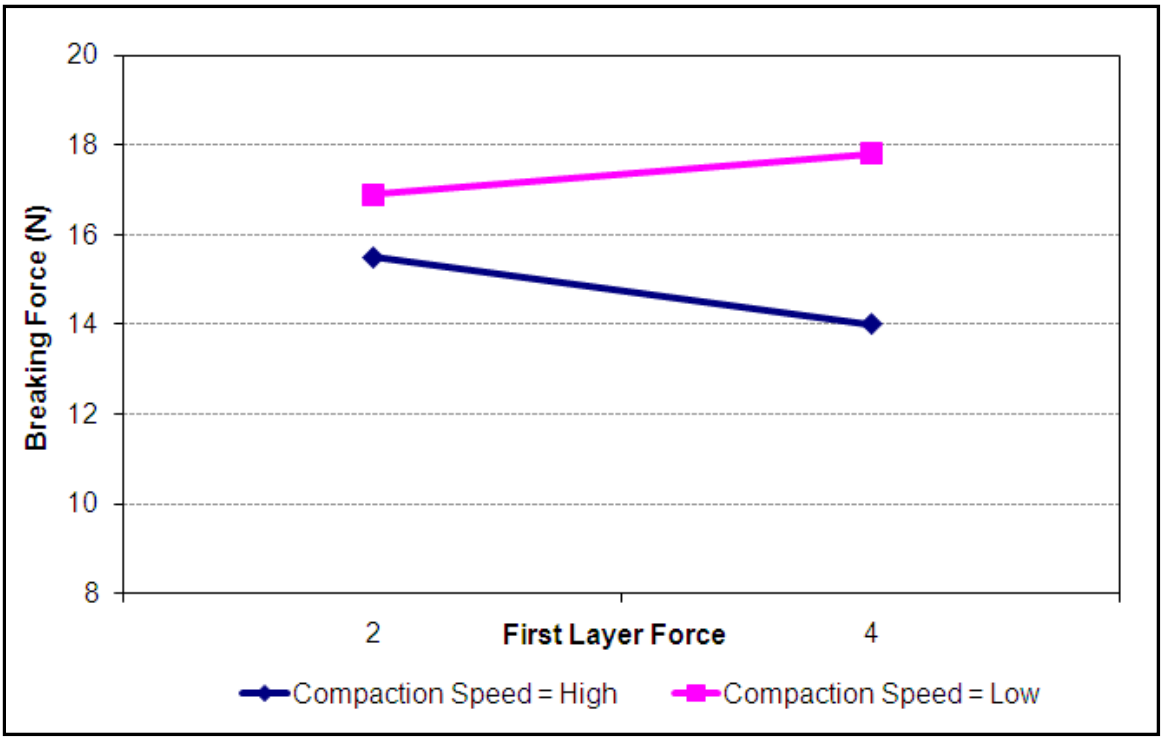


Figure 5-8: Effect of first layer force and compaction speed on the strength of lactose-avicel bilayer tablets

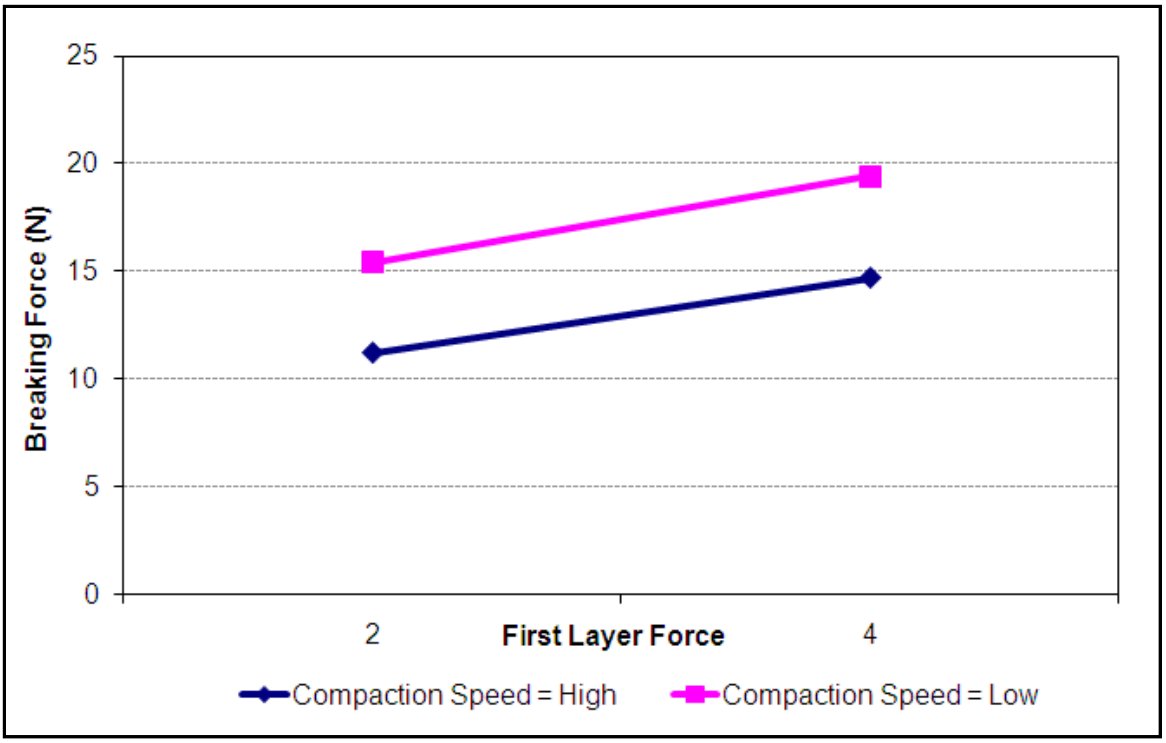


Figure 5-9: Effect of first layer force and compaction speed on the strength of Lactose-Lactose bilayer tablets

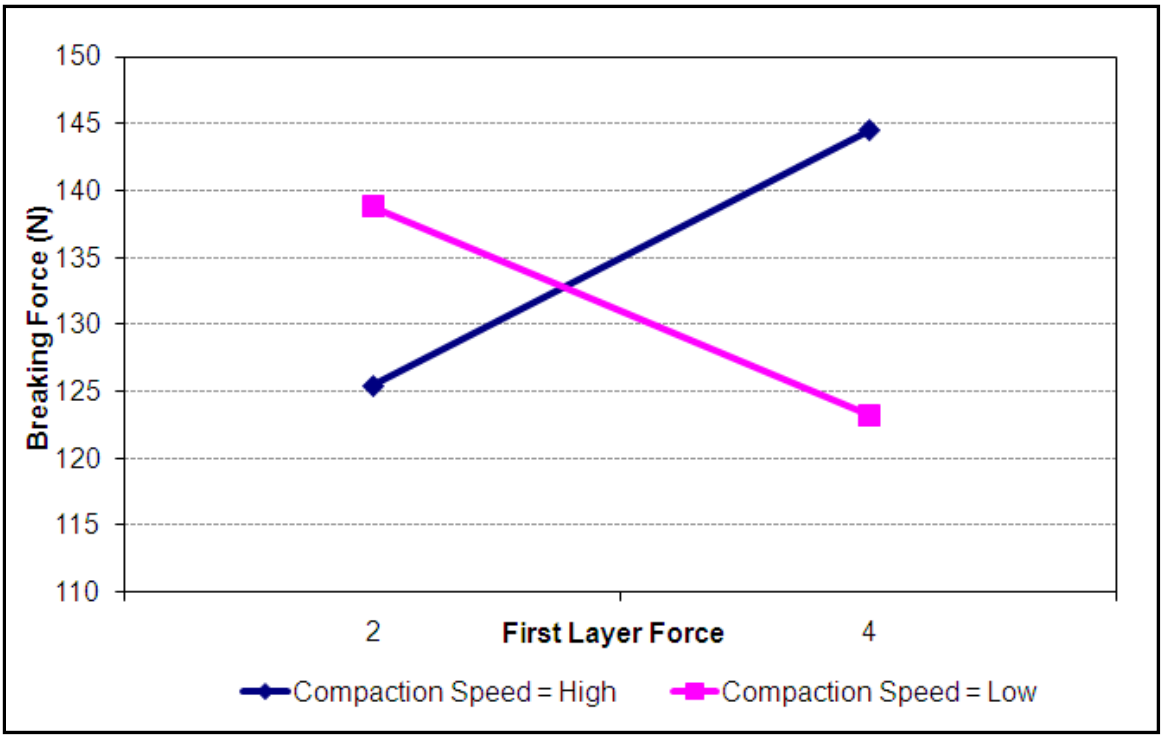


Figure 5-10: Effect of first layer force and storage time on the strength of avicel-lactose bilayer tablets

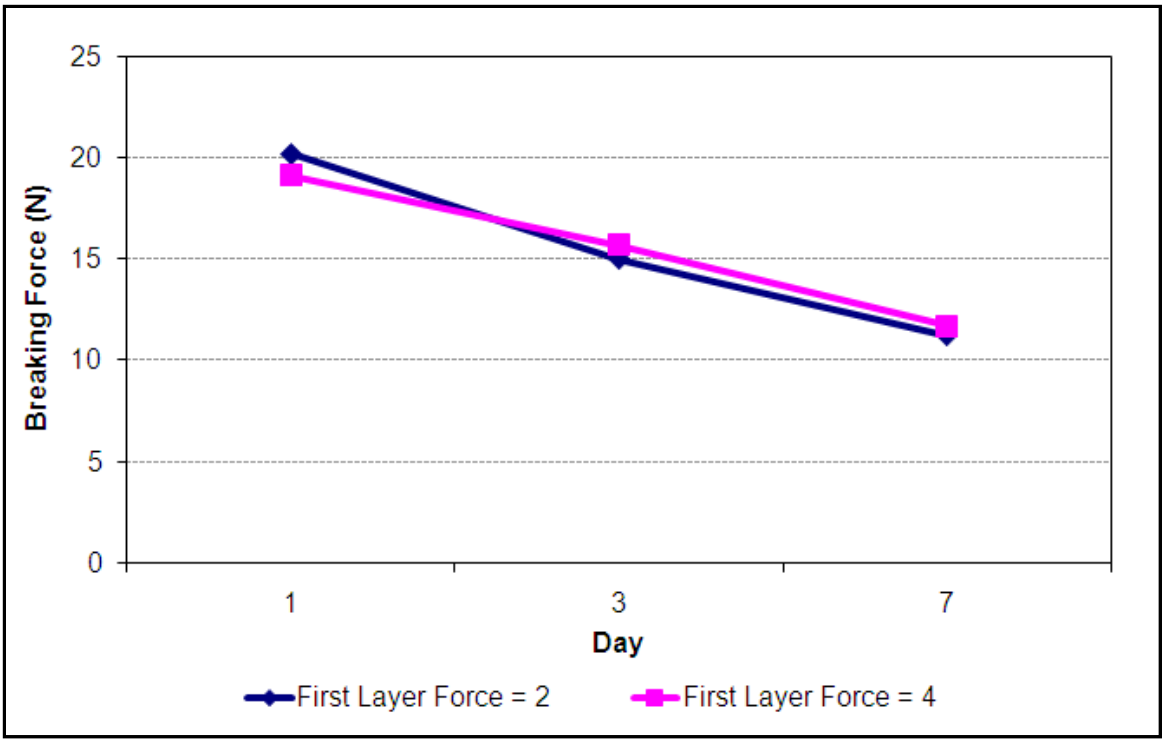


Figure 5-11: Effect of first layer force and storage time on the strength of lactose-avicel bilayer tablets

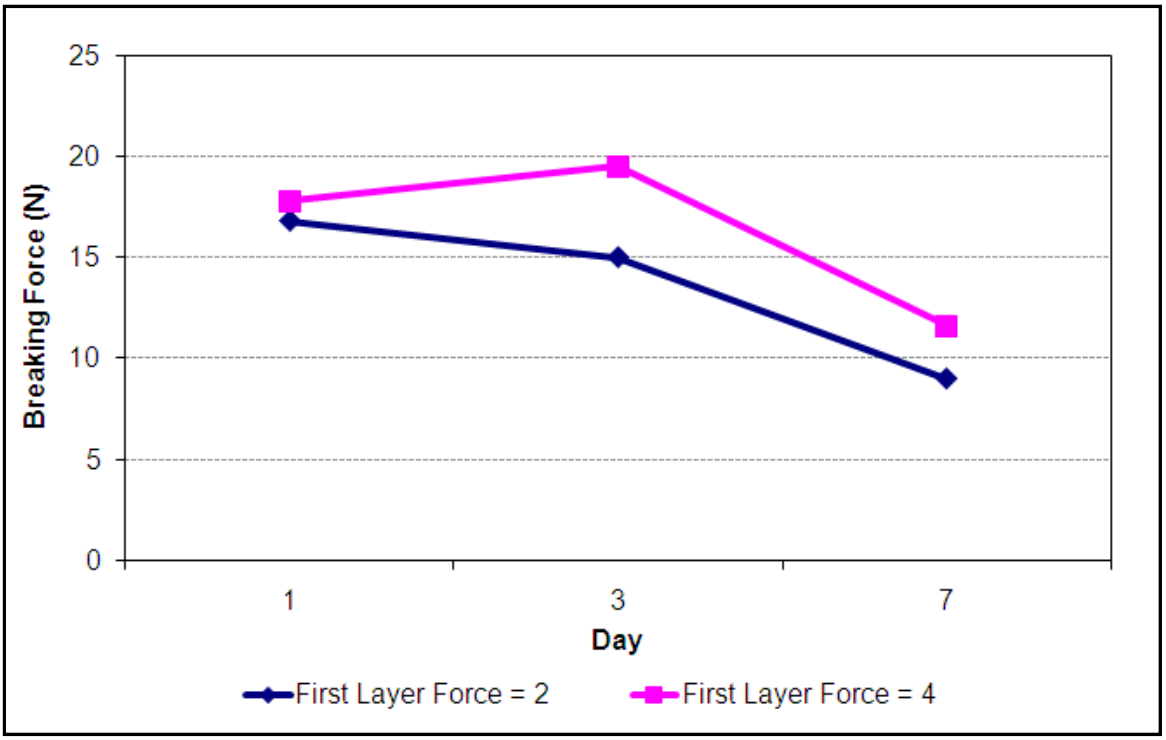


Figure 5-12: Effect of first layer force and storage time on the strength of Lactose-Lactose bilayer tablets

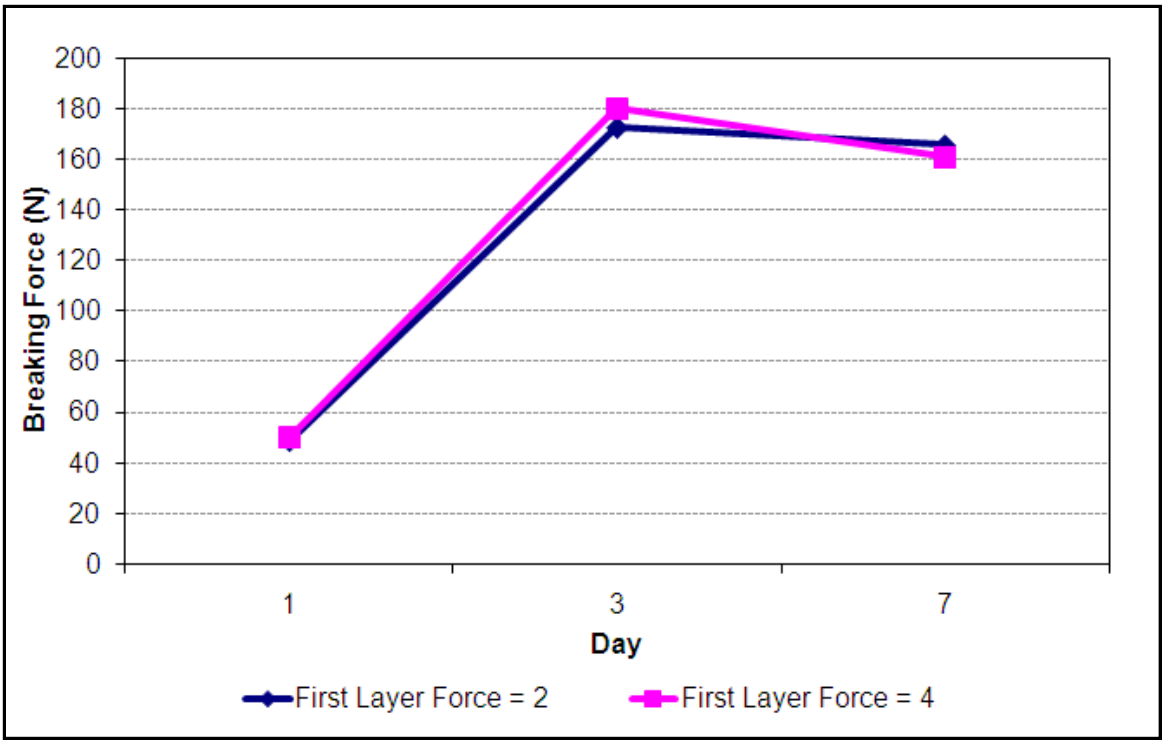


Figure 5-13: Effect of lubricant conc. and storage time on the strength of avicel-lactose bilayer tablets

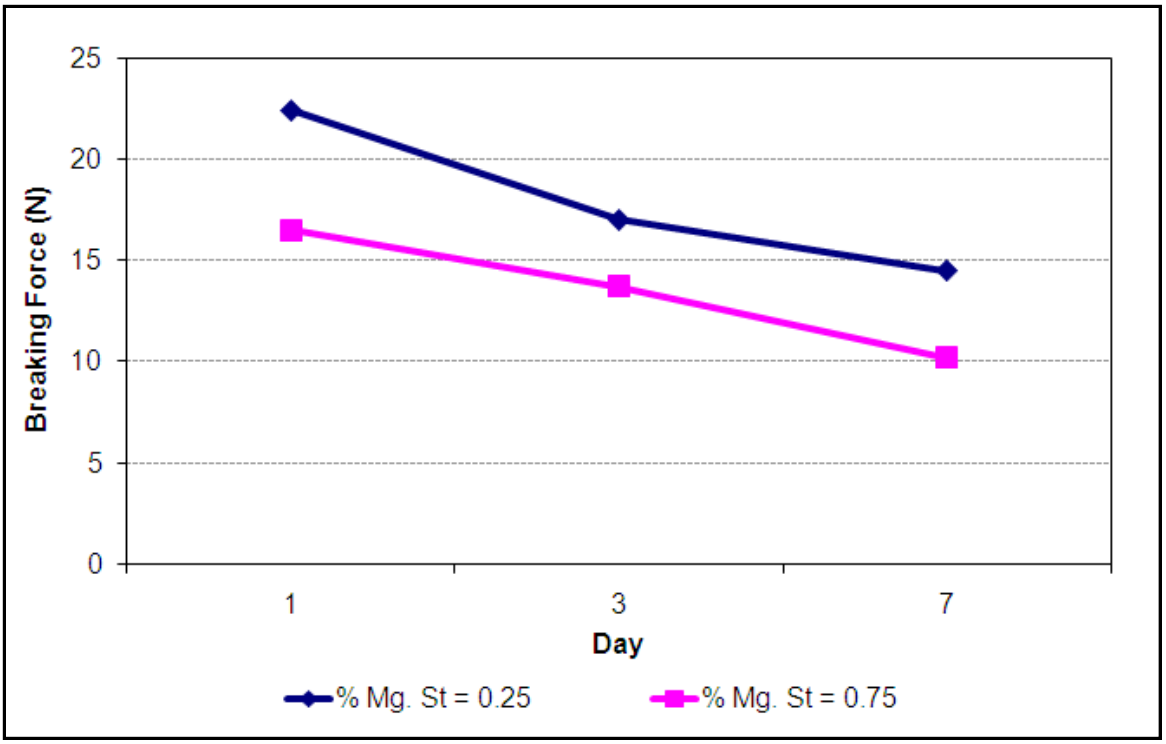


Figure 5-14: Effect of lubricant conc. and storage time on the strength of lactose-avicel bilayer tablets

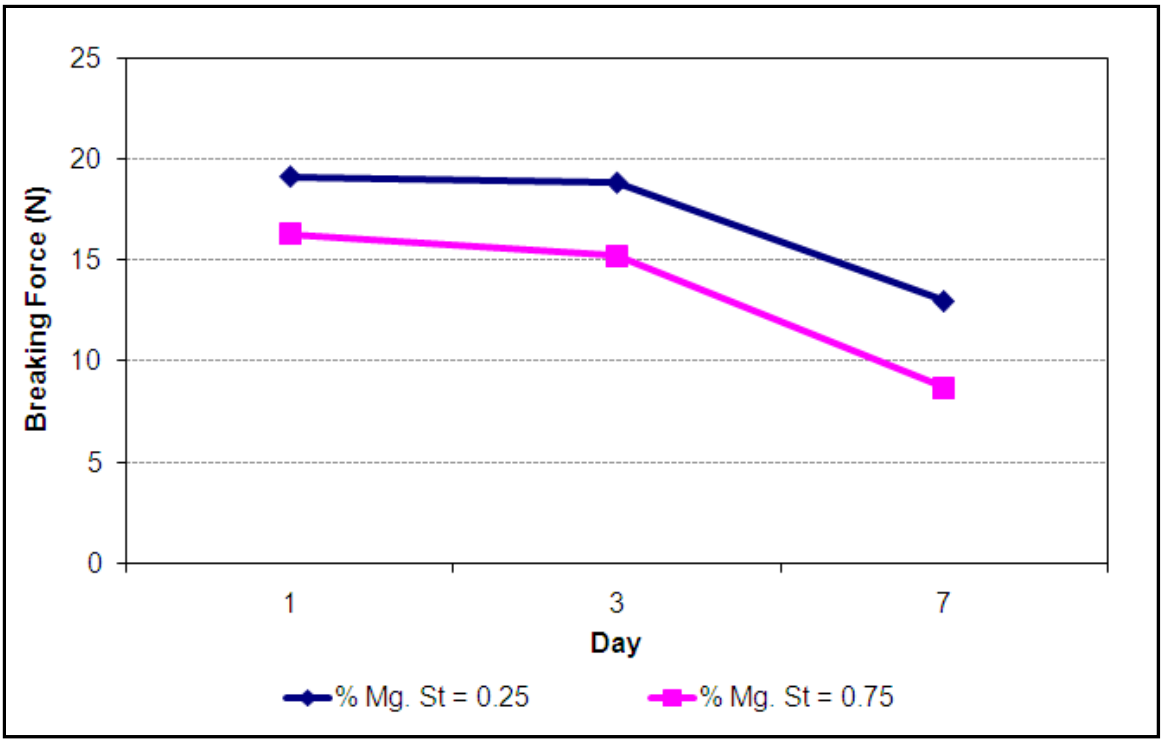


Figure 5-15: Effect of lubricant conc. and storage time on the strength of Lactose-Lactose bilayer tablets

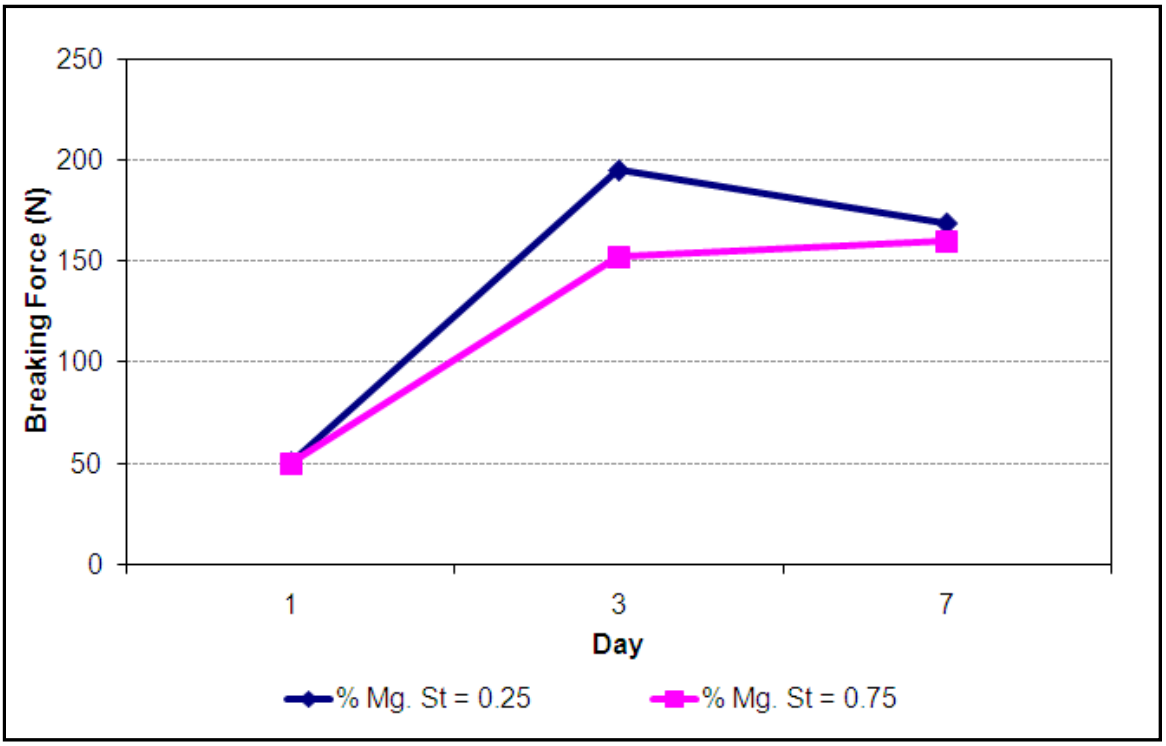


Figure 5-16: Effect of first layer force and storage time at low compaction speed on the strength of bilayer tablets

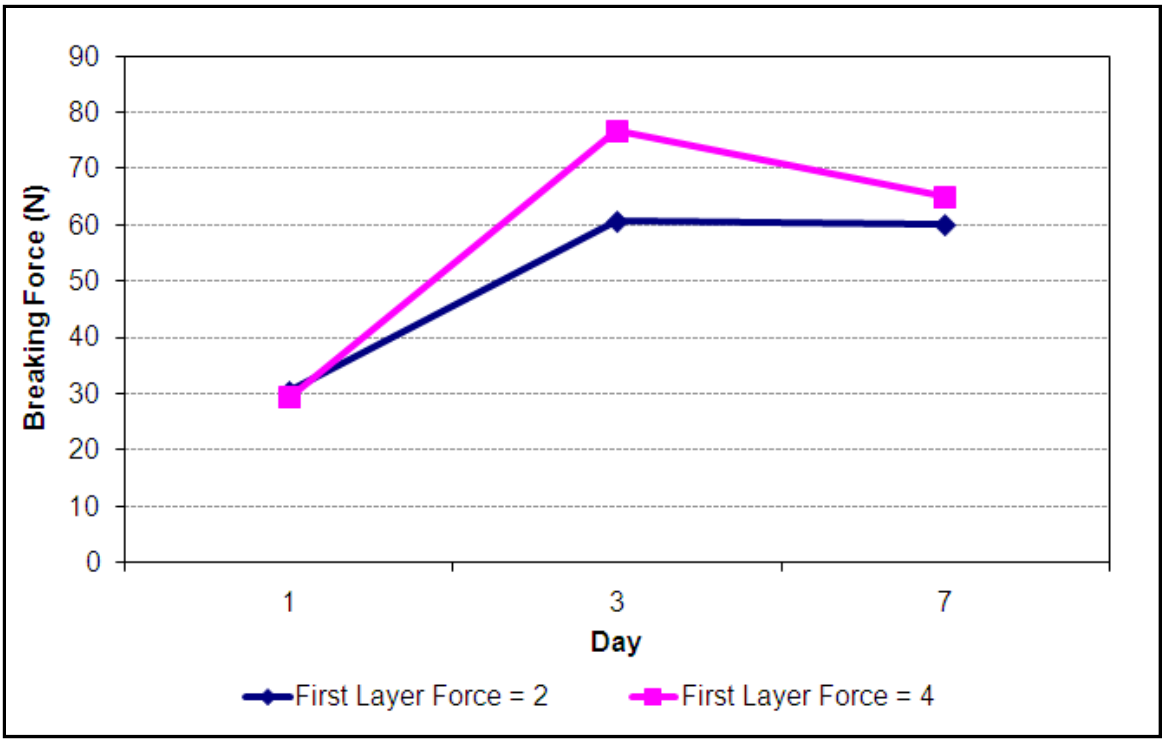
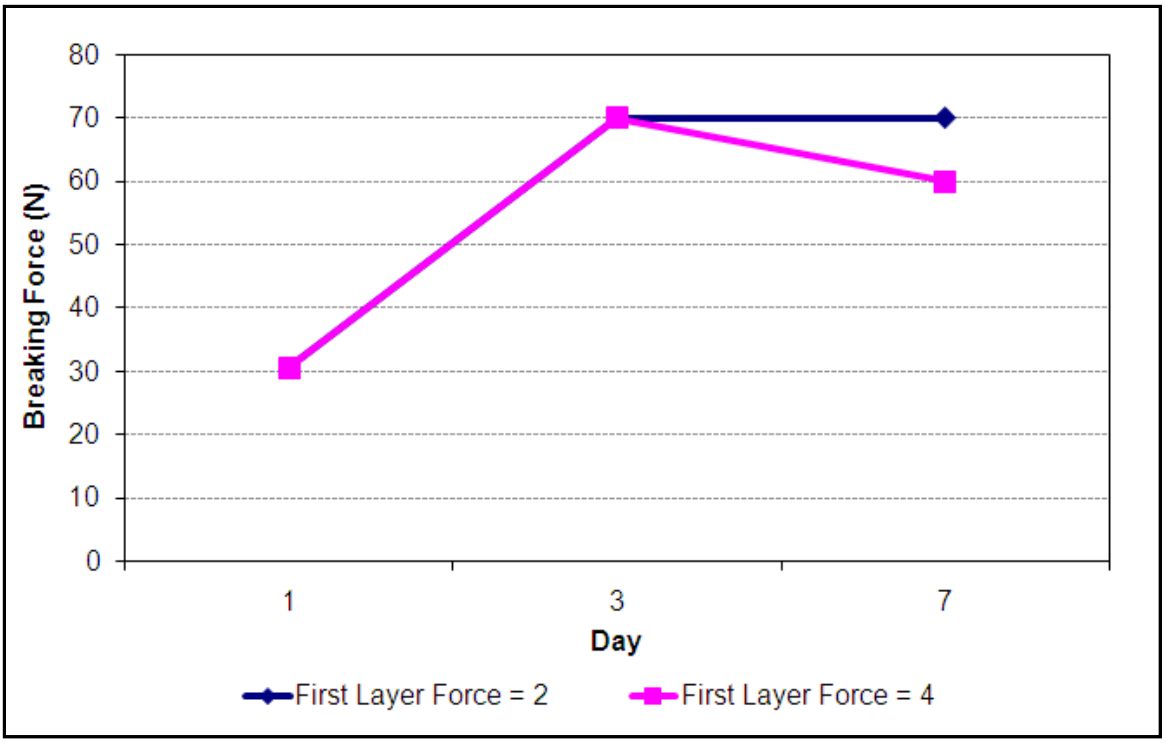


Figure 5-17: Effect of first layer force and storage time at high compaction speed on the strength of bilayer tablets



5.7 Tables for Chapter 5

Table 5-1: p-values of the different interactions.

Effect	p-Value
Day	< 0.0001
Cond	< 0.0001
Comb	< 0.0001
Compaction Speed (CS)	0.5378
Magnesium Stearate Level (MagSt)	< 0.0001
Layer 1 Compression Force (CF1)	0.2454
Day*Cond	< 0.0001
Day*Comb	< 0.0001
Day* CS	0.829
Day*MagSt	0.1024
Day*CF1	0.0293
Cond*Comb	0.4513
Cond*CS	0.1298
Cond*MagSt	0.2164
Cond*CF1	0.5132
Comb*CS	0.0358
Comb*MagSt	0.0004
Comb*CF1	0.6135
CS*MagSt	0.2772
CS*CF1	0.0009
MagSt*CF1	0.8718
Day*Cond*Comb	< 0.0001
Day*Cond*CS	0.1799
Day*Cond*MagSt	0.3723
Day*Cond*CF1	0.9708
Day*Comb*CS	0.643
Day*Comb*MagSt	0.036
Day*Comb*CF1	0.0437
Day*CS*MagSt	0.6687
Day*CS*CF1	0.0192
Day*MagSt*CF1	0.9778

Continued Table 5-1….

Effect	p-Value
Cond*Comb*CS	0.9912
Cond*Comb*MagSt	0.7489
Cond*Comb*CF1	0.0322
Cond*CS*MagSt	0.6152
Cond*CS*CF1	0.0624
Cond*MagSt*CF1	0.5889
Comb*CS*MagSt	0.3265
Comb*CS*CF1	< 0.0001
Comb*MagSt*CF1	0.7887
CS*MagSt*CF1	0.2306

† Significant Interaction

Chapter 6: Conclusions and Future Work

6.1 Conclusions

The dissertation work is divided into four specific aims. The first research aim (Chapter 2) is focused on understanding the impact of interfacial topography and deformation characteristics of the materials on the performance of bilayer tablets. As part of this endeavor novel tools were employed. Strength of bilayer tablets was characterized using an axial tester. It was shown that upon axially loading the tablets, crack has propagated along the interface for tablets made of plastic material. In the case of brittle materials breakage occurred in the first layer. The observed differences in the crack propagation modes can be attributed to the relative strengths of interface and individual layers, as crack will propagate into regions with weaker structural integrity upon loading. In the case of tablets made of plastic material individual layers are stronger than interface so the fracture occurred along the interface, where as in the case of tablets made of brittle material interfacial strength dominated the layer strength so the fracture was observed in the first layer. These differences can be attributed to the differences in the consolidation mechanisms of both the materials.

Stylus based perthometer was found to be a robust method for quantifying the interfacial roughness of the fractured tablets. A strong correlation was found between the roughness parameters R_a (average roughness), R_q (RMS roughness) and the strength of bilayer tablets. Strength of bilayer tablets increased with the increase of interfacial roughness. It was observed that both the first and second layer forces determined the magnitude of interfacial roughness for both the plastic and brittle materials.

Material properties, layer forces, and layer sequence have strongly influenced the magnitude of interfacial curvature developed at the interface during the compaction. Interfacial roughness along with the interfacial curvature provided the mechanical interlocking of the adjacent layers and hence determined the interfacial strength of tablets. The results have shown that concentration of the lubrication played a key role in influencing the strength of the bilayer tablets. For both the plastic and brittle materials, tablet strength decreased with the increase of lubricant concentration. Effect of lubricant (i.e. reduction in tablet strength with the increase of lubricant concentration) on the strength of tablets is higher for tablets made of plastic material as compared to the tablets made of brittle material.

In chapter 3, a model was developed based on the principles of fracture mechanics for the characterization of bilayer tablets. Interfacial stress intensity factor (K_I) of bilayer tablets was determined as part of this task. The influence of bilayer compression parameters, material, and interfacial properties on the interfacial stress intensity factor (K_I) was thoroughly evaluated.

The results indicated that stress intensity factor of bilayer tablets (made of plastic and brittle materials) is heavily dependent on the first layer force. Layer sequence has a strong influence on the interfacial SIF of bilayer tablets. For tablets made with same second layer force (and different layer sequence) SIF is higher for the tablets with brittle material in the first layer, and for tablets made with identical layer sequence (and different second layer force), SIF increased with the increase of second layer force.

Combination of interfacial roughness and radius of curvature have strongly influenced the ability of the interfaces to resist crack propagation. Contour plots that were generated to understand the dependency of SIF on these factors. For all the layer sequences (avicel/avicel, avicel/lactose and lactose/avicel) tablets a combination of lower interfacial radius of curvature and higher roughness of the interface has produced the tablets with highest interfacial SIF. It was also observed that for the bilayer tablets with plastic material in the first layer dependency of SIF is higher on interfacial radius of curvature compared to roughness. However, in the case of bilayer tablets with brittle material in the first layer dependency of SIF is higher on interfacial roughness compared to the interfacial radius of curvature.

Chapter 4 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. The results showed that nature of materials played a critical role on the tensile 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.

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.

In chapter 5, impact of storage conditions on the performance of bilayer tablets was evaluated. As part of this study, bilayer tablets were stored at accelerated humidity and

temperature conditions for different times. As expected, storage conditions and storage time have significant impact on the strength of bilayer tablets. For avicel-lactose and lactose-avicel tablets, tablet strength decreased with the increasing humidity and storage time. But, for lactose-lactose tablets due to the formation of solid bridges upon storage, an increase in tablet strength was observed. The effect of first layer compression force shows a strong interaction with storage condition for lactose-lactose tablets. However, for avicel-lactose and lactose-avicel tablets, effect of first layer compression force shows a slight interaction with storage condition. Compaction speed is independent of the first layer force for avicel-lactose and lactose-avicel tablets. For these tablets, a decrease in tablet strength with an increase of compaction speed was observed. There is a strong interaction between the first layer compression force and compaction speed for the lactose-lactose tablets.

6.2 Future Work

The future work can be designed on the success of the current studies in which a methodology for testing bilayer products and theoretical framework to interpret the results and models to quantify bilayer strength has been provided. The future work can be directed in two ways. One direction would involve the development of bilayer simulation platform utilizing the quasi-discrete (QD) technology followed by the model validation and calibration. Another direction would engage in the quantification of material, process and design parameters on the performance of bilayer tablets, including the task of completing a case study. In addition to the process understanding and predictive capabilities, the future work is expected to provide a methodology for exploring the design space consistent with the Quality by Design paradigm.

6.2.1 Development of Simulation Platform for Bilayer Tablets Using the Quasi-Discrete (QD) Technology

(Tensile) Strength of compacted granular solids develops during the process of consolidation due to formation of mechanical and chemical bonds among particles or granules subjected to compressive forces. Depending on the nature of the compacted materials particle bonding can occur through a variety of mechanisms. Typically, these mechanisms are distinguished based on the nature of the bonding force. Electrostatic bonding can occur due the accumulation of triboelectric charge in the powder bed or because of the presence of polar functional groups on the particles surface. Molecular force bonding, while technically also driven by electrostatic interactions is recognized as a separate mechanism due to the large difference in separation scales, at which the two phenomena manifest. Caused by van der Waals type interactions between charged or polarized molecules, molecular force bonding requires the powder particles to be in extremely close contact. In the presence of humidity, liquid menisci can form between particles leading to attractive forces proportional to the surface tension of the liquid. Finally, during prolonged contact between particles, solid bridges can form due to material melting, self-diffusion of atoms and recrystallization. For most typical pharmaceutical excipients, bonding is due to only occur by virtue of molecular forces and the formation of solid bridges.

A proper estimate of the mechanical strength of a compacted solid is contingent upon the knowledge of the amount of ***inter-particle contact*** area created during the plastic deformation stage of the compression. A coupling between a modeling tool capable of

capturing the local deformations occurring during the densification of the bed and a bonding force formulation consistent with the physical inter-particle interactions is therefore necessary to adequately apply *Quality by Design* **(QbD)** principles to the process of powder compaction.

The first part of the future work engages in developing a modeling and simulation platform to predict the development of the overall compact strength due to each individual granule-bonding event during the manufacturing process. This new modeling *Quasi-Discrete* (QD) methodology (Figure 6-1) combines both discrete and continuum aspects of the problem, and so is particularly well suited for the study the bonding during compaction.

As part of this objective, a simulation platform will be developed using the *quasi-discrete* methodology for predicting the interfacial strength of bilayer tablets by accounting the granule level properties (e.g. particle side distribution, surface coating), inter-granular properties (e.g. interlayer roughness) and tablet level properties (e.g. shape, layer thickness) (Figure 6-2). This simulation platform will enable us to perform the following tasks:

- generate different geometries of bilayer tablets including the shape, layer thickness and flat or curve surfaces,
- generate different granular materials for the each layer including particle size distribution, elastic and plastic properties,
- apply different loading to each layer (variable tapping force),

- track the deformation history of each layer including the contact area and bonding among granules during loading and unloading
- account for the frictional effects among the die wall and punches

As part of this endeavor, we will also validate the simulation predictions against a set of model materials utilizing the tensile testing methodology and the extensive database available from the design of experiments (DOE) developed as part of the current effort. We will develop a methodology to determine the model parameters from the independent measurements, such as PSD, elastic moduli, etc.

6.2.2 Quantification of Material, Process and Design Parameters on the Performance of Bilayer Tablets

The second part of the future work involves the computational evaluation of the impact of material properties and process variables on the overall performance of the bilayer interfacial strength. For each case study the maximum local interracial strength and the total energy of delamination can be computed using the QD methodology. Each case requires a significant computational effort where a 3D numerical calculation with a large number of cells and granules needs to be performed. The following cases can be considered:

6.2.2.1 Effect of granule elastic properties (material parameter)

As the stress fields play a vital role on the load transfer from the top to the bottom layer, a numerical study should be executed to evaluate the role of formulation (elastic) properties of each layer on the stress distribution in the interfacial area.

For a given geometry following two cases can be considered:

Case1: Soft bottom layer and hard top layer and

Case2: Hard bottom layer and soft top layer.

These two cases can be used as reference (as baseline stress fields) for subsequent studies.

6.2.2.2 Effect of granule plastic properties (material parameter)

The plastic behavior of the granules play a key role in the process of bonding, as the plasticity is the main mechanisms for increasing the contact surface and promoting bonding. The two main parameters that define the plastic behavior are: yield stress (Y), which characterizes the initiation of plastic deformation and hardening (H) which describes the post yielding response. Simulations can be executed (for the cases shown in table 6-1) to evaluate the effect of these two parameters for each layer, and the overall impact on the performance of the bilayer tablets.

6.2.2.3 Effect of First Layer Force and Compaction Force (process parameter)

Experimental studies carried out as part of this thesis has shown that the compaction force (tractions) applied to the first layer are an extremely important variable controlling the interfacial strength in a nontrivial manner. In fact, increasing the first layer force shows an increase of the interfacial strength for all values of the final compaction forces up to a critical value, followed by a monotonic decrease afterwards. The quantification of the level of compaction in the first layer for different conditions is a key manufacturing factor and offers an opportunity to select a range of conditions to maximize the interfacial

strength of bilayer tablets. From the previous task 6.2.2.2, we will study two cases with the highest and lowest predicted interfacial strength. For these two cases, we can consider the 9 (x2) conditions indicated in the table 6-2.

6.2.2.4 Effect of Ejection Forces

During the ejection process large stress field transient can prematurely damage the newly formed bilayer interface, weakening the overall performance of the bilayer tablet. Selecting from the most extreme cases from the task 6.2.2.2, we can study the stresses on the interface (driving force for delamination) during the ejection, which will results as in the task 6.2.2.3, in 9(x2) ejection simulations.

6.2.2.5 Effect of Friction (material/process parameter)

Friction modulates the spatial variations during the first layer compaction, second layer compaction and ejection. If no friction is present in a cylindrical tablet, all stress fields will not have spatial variations resulting in one-dimensional problem. For all previous cases, a constant level of friction will necessarily be included. In this task, however, we will concentrate on quantifying the effect of different level of friction on the variation of the stress fields and more importantly on the resulting curvature at the interface between the top and the bottom layer. For the same two cases of task 6.2.2.4, we can consider three levels of friction (low ~ 0.1, medium ~0.3 and high ~0.6) to understand its impact on the bilayer interfacial strength.

6.2.2.6 Effect of Tablet Dimensions/Shape (design parameter)

Manufacturing of non-cylindrical shape tablets, is a common practice in the pharmaceutical industry, tablet shapes are prone to develop large stress gradient during compaction and ejection, affecting particularly the strength of bilayer products. To evaluate the effect of the non-flat punches on the stress field during the compaction and ejection, three different punch curvatures will be considered utilizing the two extreme material cases of task 6.2.2.2 and the medium level of friction of case 6.2.2.5.

6.3 Figures for Chapter 6

Figure 6-1: Quasi-discrete simulation engine. [Source: I. Akseli et al., 2010]
(Colors from red to blue indicate the degree of granule to granule bonding)

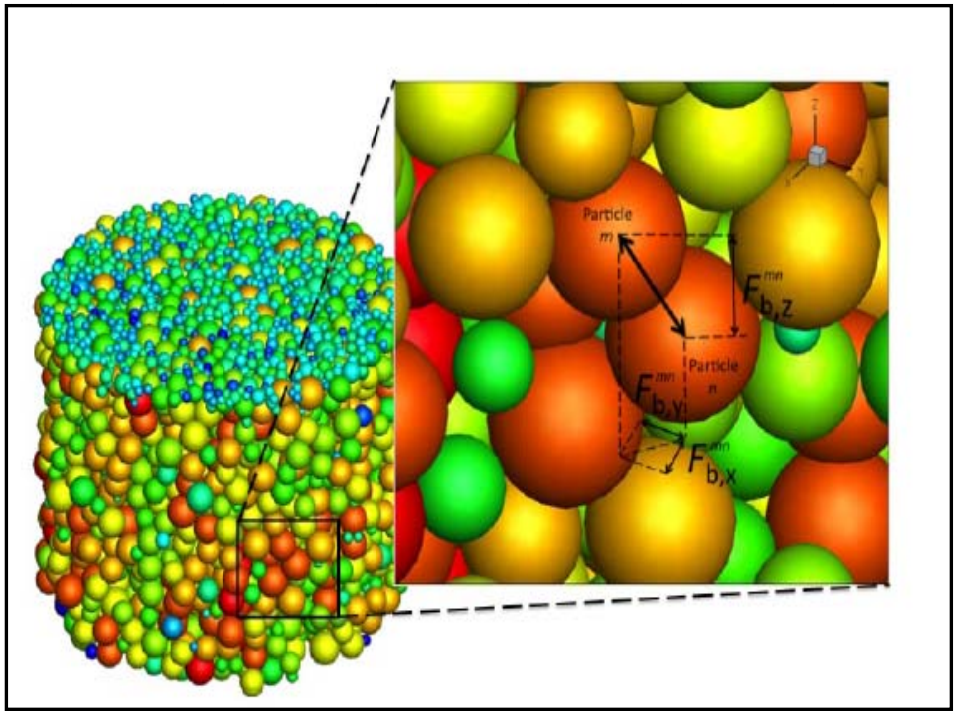
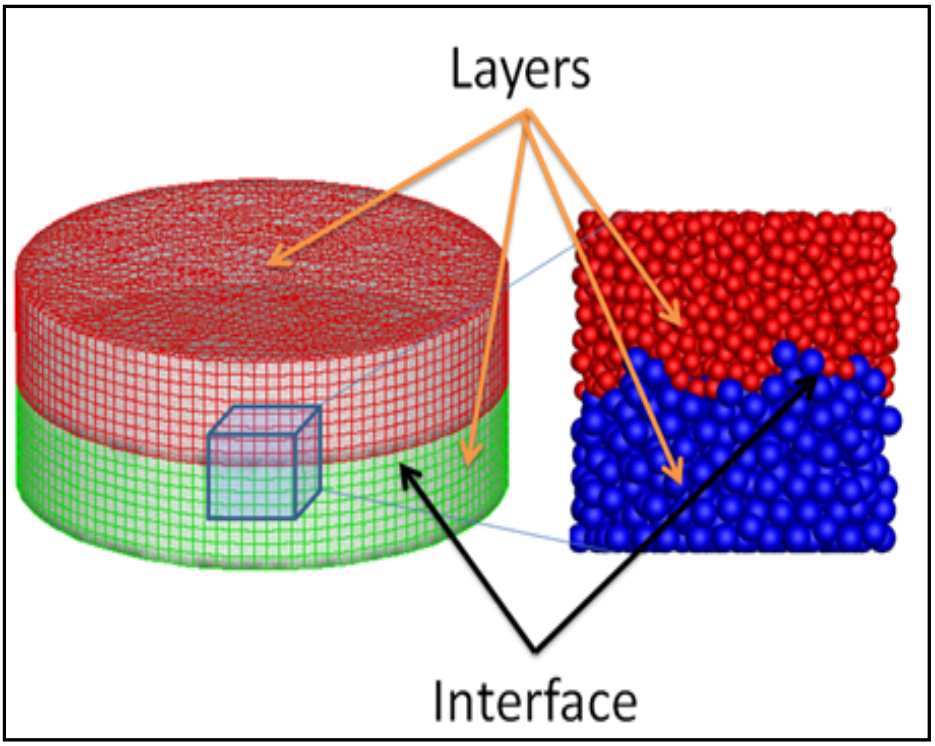


Figure 6-2: Bilayer Simulation Platform utilizing *Quasi-Discrete* QD engine. [Source: I. Akseli et al., 2010]



6.4 Tables for Chapter 6

Table 6-1: Simulation plan for evaluating the effect of granule plastic properties
[Source: A. Cuitino, 2012]

Plastic Cases		Top Layer			
		Low Y Low H	Low Y High H	High Y Low H	High Y High H
Bottom Layer	Low Y Low H	Case 1	Case 2	Case 3	Case 4
	Low Y High H	Case 5	Case 6	Case 7	Case 8
	High Y Low H	Case 9	Case 10	Case 11	Case 12
	High Y High H	Case 13	Case 14	Case 15	Case 16

Table 6-2: Simulation plan for evaluating the effect of layer forces
[Source: A. Cuitino, 2012]

Applied Forces		First Layer Force		
		Low	Medium	High
Compaction Force	Low	Case 1	Case 2	Case 3
	Medium	Case 4	Case 5	Case 6
	High	Case 7	Case 8	Case 9

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Appendix A

DOE for evaluating the impact of material properties and manufacturing process parameters on the tensile strength of bilayer tablets.

		First Layer		Second Layer				
#	Breaking Force (N)	Excipient	Compression Force	Excipient	Compression Force	Second: First Excipient Weight Ratio	Compaction Speed (rpm)	% Mg. St
1	0	Avicel	3kN	Avicel	18kN	1:1	15	0.50
2	159	Lactose	2kN	Lactose	14kN	1:3	10	0.25
3	0	Avicel	4kN	Avicel	22kN	3:1	20	0.25
4	8	Avicel	2kN	Lactose	14kN	3:1	20	0.75
5	0	Avicel	2kN	Avicel	14kN	1:3	20	0.75
6	11	Avicel	2kN	Lactose	14kN	1:3	10	0.75
7	36	Avicel	2kN	Lactose	14kN	3:1	10	0.25
8	118	Lactose	3kN	Lactose	18kN	1:1	15	0.50
9	12	Avicel	2kN	Lactose	22kN	3:1	10	0.75
10	0	Avicel	2kN	Avicel	14kN	3:1	20	0.25
11	25	Lactose	2kN	Avicel	22kN	1:3	20	0.75
12	34	Lactose	3kN	Avicel	18kN	1:1	15	0.50
13	76	Lactose	2kN	Lactose	14kN	3:1	20	0.25
14	37	Lactose	2kN	Avicel	22kN	3:1	20	0.25
15	19	Lactose	4kN	Avicel	14kN	1:3	10	0.25
16	0	Avicel	2kN	Avicel	22kN	1:3	20	0.25
17	121	Lactose	2kN	Lactose	22kN	1:3	10	0.75
18	21	Avicel	4kN	Lactose	22kN	1:3	10	0.75
19	88	Lactose	4kN	Lactose	14kN	3:1	20	0.75
20	6	Avicel	4kN	Lactose	22kN	3:1	20	0.75
21	65	Lactose	4kN	Lactose	22kN	3:1	20	0.25
22	92	Lactose	4kN	Lactose	14kN	3:1	10	0.25
23	25	Lactose	2kN	Lactose	22kN	3:1	20	0.75
24	0	Avicel	4kN	Avicel	22kN	1:3	20	0.75
25	27	Lactose	4kN	Avicel	22kN	3:1	10	0.25
26	121	Lactose	2kN	Lactose	22kN	3:1	10	0.25
27	0	Avicel	4kN	Avicel	14kN	1:3	10	0.75
28	14	Lactose	4kN	Avicel	14kN	3:1	10	0.75
29	21	Avicel	4kN	Lactose	22kN	1:3	20	0.25
30	21	Lactose	2kN	Avicel	14kN	3:1	20	0.75
31	127	Lactose	2kN	Lactose	14kN	3:1	10	0.75
32	20	Lactose	4kN	Lactose	22kN	1:3	20	0.75
33	29	Avicel	4kN	Lactose	14kN	3:1	20	0.25
34	42	Avicel	4kN	Lactose	22kN	3:1	10	0.25
35	29	Lactose	2kN	Avicel	14kN	3:1	10	0.25
36	29	Lactose	2kN	Avicel	22kN	1:3	10	0.25

37	0	Avicel	2kN	Avicel	14kN	1:3	10	0.25
38	101	Lactose	4kN	Lactose	14kN	1:3	20	0.25
39	31	Lactose	4kN	Avicel	22kN	1:3	20	0.25
40	0	Avicel	2kN	Avicel	22kN	1:3	10	0.75
41	102	Lactose	3kN	Lactose	18kN	1:1	15	0.50
42	0	Avicel	4kN	Avicel	22kN	3:1	10	0.75
43	118	Lactose	2kN	Lactose	22kN	1:3	20	0.25
44	45	Avicel	2kN	Lactose	22kN	1:3	10	0.25
45	28	Avicel	4kN	Lactose	14kN	1:3	10	0.25
46	0	Avicel	3kN	Avicel	18kN	1:1	15	0.50
47	0	Avicel	4kN	Avicel	14kN	3:1	20	0.75
48	6	Avicel	4kN	Lactose	14kN	1:3	20	0.75
49	4	Lactose	4kN	Avicel	14kN	1:3	20	0.75
50	5	Avicel	3kN	Lactose	18kN	1:1	15	0.50
51	16	Avicel	2kN	Lactose	14kN	1:3	20	0.25
52	136	Lactose	4kN	Lactose	14kN	1:3	10	0.75
53	49	Avicel	2kN	Lactose	22kN	3:1	20	0.25
54	0	Avicel	2kN	Avicel	22kN	3:1	10	0.25
55	19	Avicel	2kN	Lactose	22kN	1:3	20	0.75
56	0	Avicel	4kN	Avicel	14kN	1:3	20	0.25
57	108	Lactose	4kN	Lactose	22kN	3:1	10	0.75
58	41	Lactose	2kN	Avicel	14kN	1:3	20	0.25
59	85	Lactose	4kN	Lactose	22kN	1:3	10	0.25
60	0	Avicel	4kN	Avicel	14kN	3:1	10	0.25
61	5	Lactose	4kN	Avicel	22kN	3:1	20	0.75
62	25	Lactose	3kN	Avicel	18kN	1:1	15	0.50
63	24	Lactose	4kN	Avicel	22kN	1:3	10	0.75
64	7	Avicel	3kN	Lactose	18kN	1:1	15	0.50
65	75	Lactose	2kN	Lactose	14kN	1:3	20	0.75
66	4	Avicel	4kN	Lactose	14kN	3:1	10	0.75
67	0	Avicel	2kN	Avicel	22kN	3:1	20	0.75
68	33	Lactose	4kN	Avicel	14kN	3:1	20	0.25
69	24	Lactose	2kN	Avicel	14kN	1:3	10	0.75
70	0	Avicel	2kN	Avicel	14kN	3:1	10	0.75
71	30	Lactose	2kN	Avicel	22kN	3:1	10	0.75
72	0	Avicel	4kN	Avicel	22kN	1:3	10	0.25

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