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Research Article

Evaluation of the Performance Characteristics of Bilayer Tablets: Part II. Impact of Environmental Conditions on the Strength of Bilayer Tablets

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Abstract. Ambient air humidity and temperature are known to influence the mechanical strength of tablets. The objective of this work is to understand the influence of processing parameters and environmental conditions (humidity and temperature) on the strength of bilayer tablets. As part of this study, bilayer tablets were compressed with different layer ratios, dwell times, layer sequences, material properties (plastic and brittle), first and second layer forces, and lubricant concentrations. Compressed tablets were stored in stability chambers controlled at predetermined conditions (40C/45%RH, 40C/75%RH) for 1, 3, and 5 days. The axial strength of the stored tablets was measured and a statistical model was developed to determine the effects of the aforementioned factors on the strength of bilayer tablets. As part of this endeavor, a full 3×2^4 factorial design was executed. Responses of the experiments were analyzed using PROC GLM of SAS (SAS Institute Inc, Cary, North Carolina, USA). A model was fit using all the responses to determine the significant interactions ($p<0.05$). Results of this study indicated that 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. Significant interactions were observed between processing parameters and storage conditions on the strength of bilayer tablets.

KEY WORDS: axial tester; bilayer tablet; design of experiments; storage conditions; tablet strength.

INTRODUCTION

Bilayer tablets are gaining more popularity recently as they offer several advantages over conventional tablets. Key advantages include reducing pill burden by administering two or more active pharmaceutical ingredients (1), prolonging the patent life of a drug product (2), increased efficacy of the active components due to their additive or synergistic effect (3), reduced toxicity (4), improved adherence to treatment regimens by patients (5), and convenience of use (1). 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.* (6) 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 (7) reported that upon storage, surface area for sodium chloride remained almost constant but the tablet strength increased by twofold in a short time. Bolhuis *et al.* (8) observed that upon storage at higher humidity, tablet strength and Brunauer, Emmett, and Teller (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

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in the tablets by sorbed moisture. Lerk (9) 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.* (10) 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 postcompaction 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 postcompaction strength changes of nonhygroscopic pharmaceutical materials. For these materials, postcompaction 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.* (11) have shown that postcompaction 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 increased surface area for interparticulate attractions. Hall *et al.* (12) 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 postcompaction changes in the tablet strength due to adsorption of moisture, it is of interest to study the relationship between the mechanical strength and the postcompaction 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 laboratory scale, and only the impact of material properties on the tablet strength upon storage was evaluated. This paper 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.

MATERIALS AND METHODS

The materials and methods used to prepare and test the bilayer tablets have been described in Part I of this paper (13).

Table I. *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
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

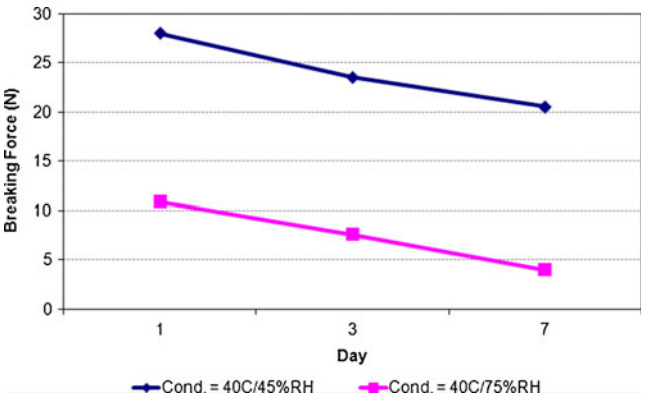

Fig. 1. Effect of storage condition and storage time on the strength of Avicel-Lactose bilayer tablets

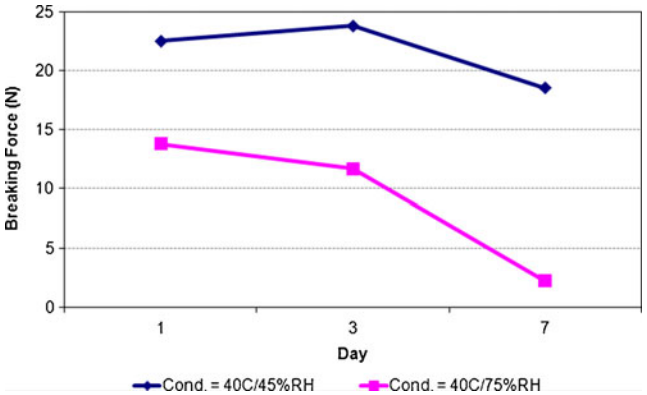

Fig. 2. Effect of storage condition and storage time on the strength of Lactose-Avicel bilayer tablets

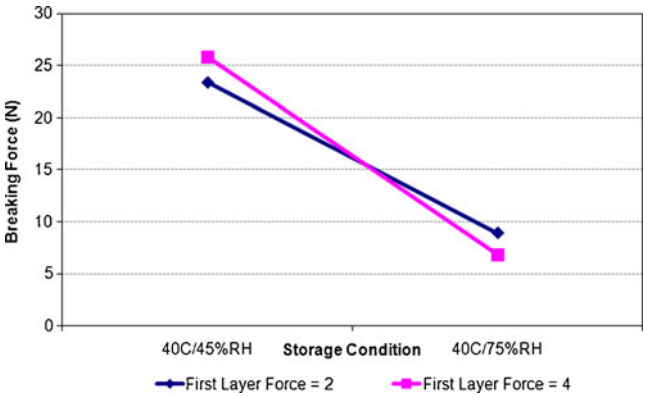

Fig. 4. Effect of first layer force and storage condition on the strength of Avicel-Lactose bilayer tablets

Statistical Design of Experiments

A full 3×2^4 factorial design was used to evaluate the effects of storage condition, first/second layer excipient combination, dwell time, magnesium stearate 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:

1. *Storage condition*: two levels (40C/45%RH, 40C/75%RH)
2. *First/second layer excipient combinations*: three levels (lactose/Avicel, lactose/lactose, Avicel/lactose)
3. *Compaction speed*: two levels (10, 20 rpm)
4. *Magnesium stearate*: two levels (0.25%, 0.75%)
5. *First layer compression force*: two levels (2, 4 kN)

RESULTS AND DISCUSSION

Effects of the six factors (storage condition, first/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, USA). A model was fit that contained the six main effects, 15 two-way interactions and 20 three-way interactions. Table I 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 measured breaking force ranged from 0 to 296 N. The root mean square estimate (random error) from the full model is 8.75 N

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 plotted and discussed in the following sections. This includes the Day×Cond×Comb, Day×Comb×MgSt, Day×Comb×CF1, Day×DT×CF1, Condition×Comb×CF1, and Comb×DT×CF1 three-way interactions.

Effect of Storage Conditions and Time On The Strength Of Bilayer Tablets

For Avicel–lactose (Fig. 1) and lactose–Avicel (Fig. 2) tablets, increasing humidity lowers tablet strength with a similar difference at days1 and 3. The effect is greater for lactose–Avicel at day7. 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 (14).

For lactose–lactose (Fig. 3) tablets, there is a significant interaction between time and humidity level. Increasing humidity increases tablet strength at days1 and

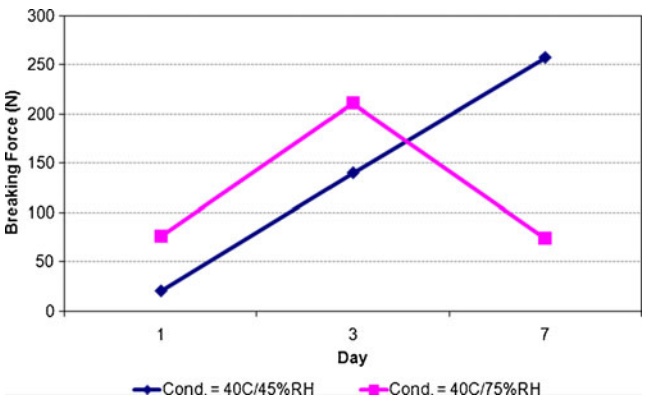

Fig. 3. Effect of storage condition and storage time on the strength of Lactose-Lactose bilayer tablets

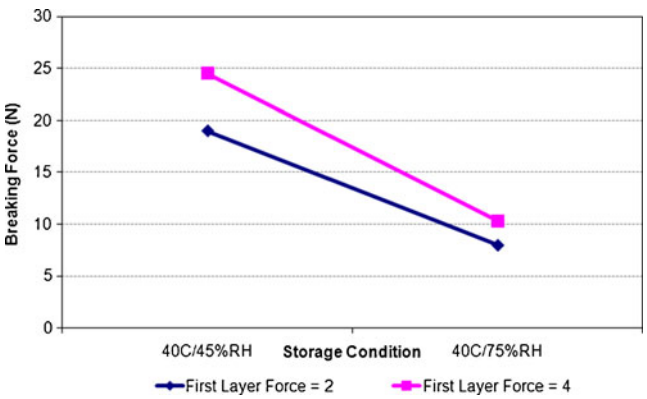

Fig. 5. Effect of first layer force and storage condition on the strength of Lactose-Avicel bilayer tablets

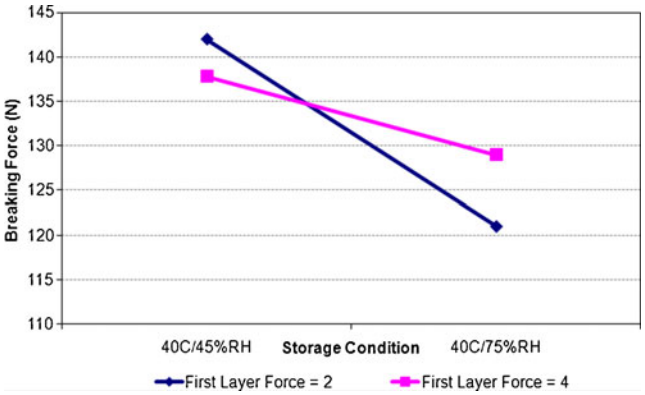

Fig. 6. Effect of first layer force and storage condition on the strength of Lactose-Lactose bilayer tablets

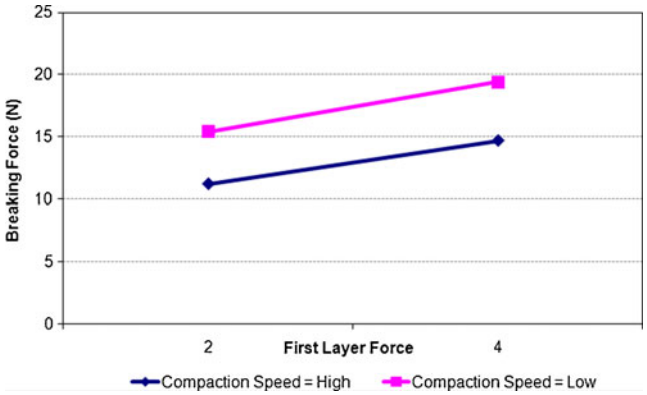

Fig. 8. Effect of first layer force and compaction speed on the strength of Lactose-Avicel bilayer tablets

3, but reduces tablet strength at day7. There is an upward trend at both humidity conditions from days1 to 7. The lower humidity condition continues to increase until day7 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 days1 to 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 days 3 to 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.

Effect of First Layer Force and Storage Condition On The Strength Of Bilayer Tablets

For all three material combinations (Figs. 4, 5, and 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 (Fig. 4) and lactose–Avicel (Fig. 5) bilayer tablets, but the dependence of the storage condition effect on the first layer force is small.

For lactose–lactose (Fig. 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 on the 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.

Effect of First Layer Force and Compaction Speed on the Strength of Bilayer Tablets

As shown in Figs. 7 and 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

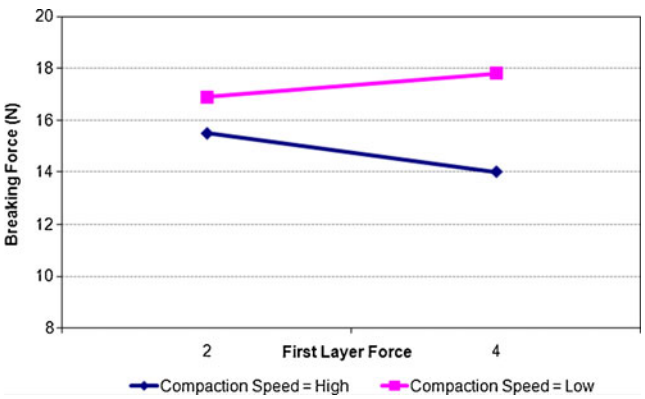

Fig. 7. Effect of first layer force and compaction speed on the strength of Avicel-Lactose bilayer tablets

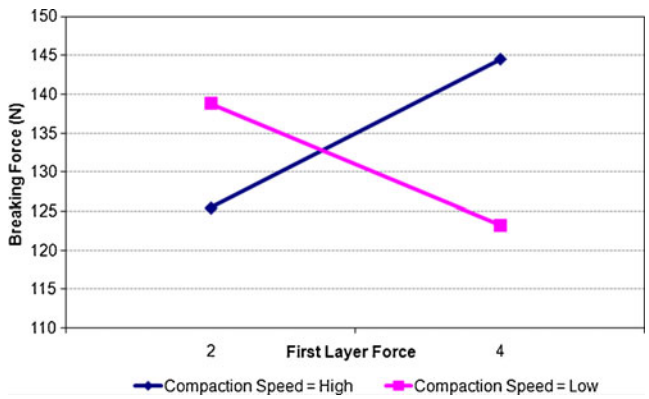

Fig. 9. Effect of first layer force and compaction speed on the strength of Lactose-Lactose bilayer tablets

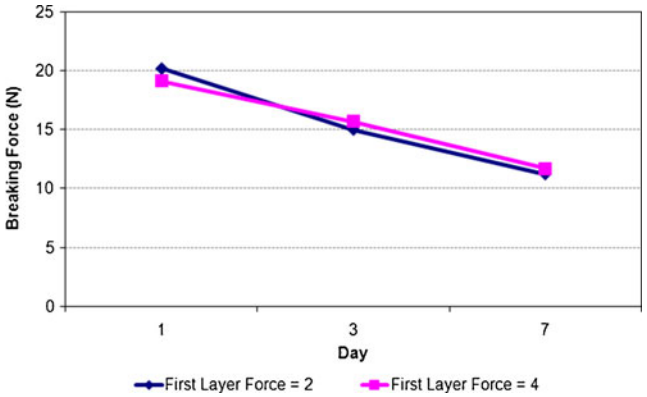

Fig. 10. Effect of first layer force and storage time on the strength of Avicel-Lactose bilayer tablets

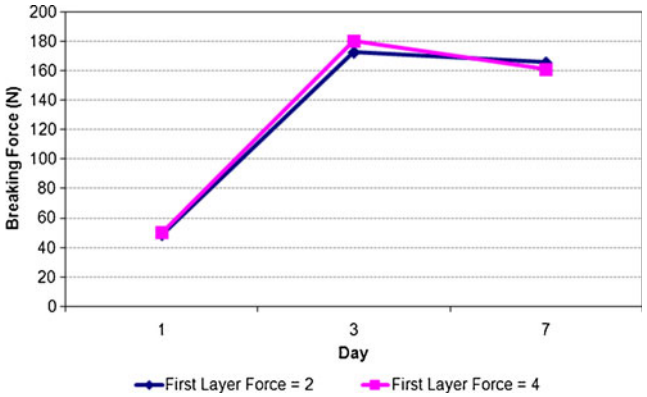

Fig. 12. Effect of first layer force and storage time on the strength of Lactose-Lactose bilayer tablets

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 (Fig. 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.*. (15), 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.

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

For Avicel–lactose tablets (Fig. 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 Fig. 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 days3 and 7 than at day1. 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 Fig. 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 days 1 to 3 upon storage at and remained constant till day7. The increase in tablet strength upon storage can be attributed to the recrystallization of amorphous lactose and formation of strong solid bridges.

Effect of Magnesium Stearate and Storage Time on Strength of Bilayer Tablets

Tablet strength decreased with the increase of magnesium stearate content for all three material combinations.

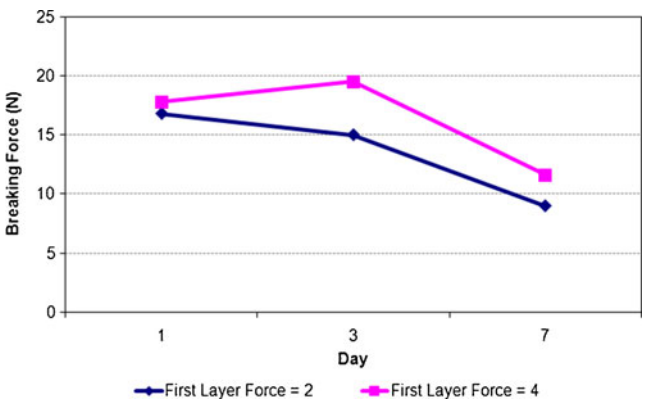

Fig. 11. Effect of first layer force and storage time on the strength of Lactose-Avicel bilayer tablets

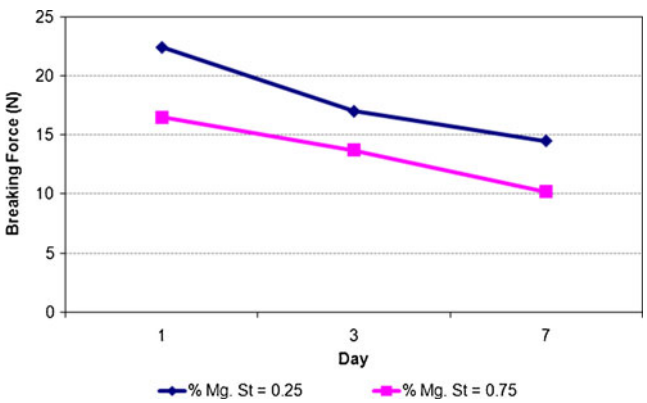

Fig. 13. Effect of lubricant conc. and storage time on the strength of Avicel-Lactose bilayer tablets

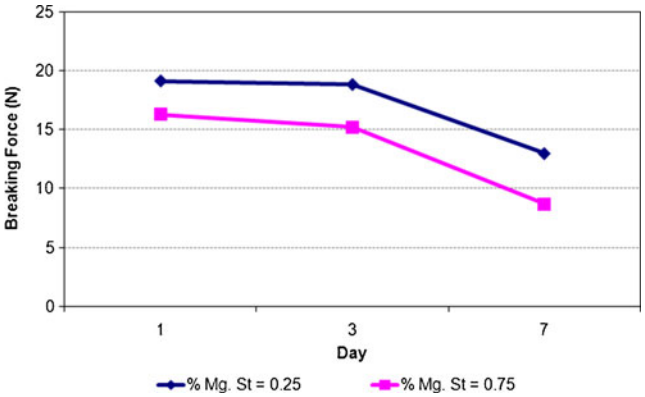

Fig. 14. Effect of lubricant conc. and storage time on the strength of Lactose-Avicel bilayer tablets

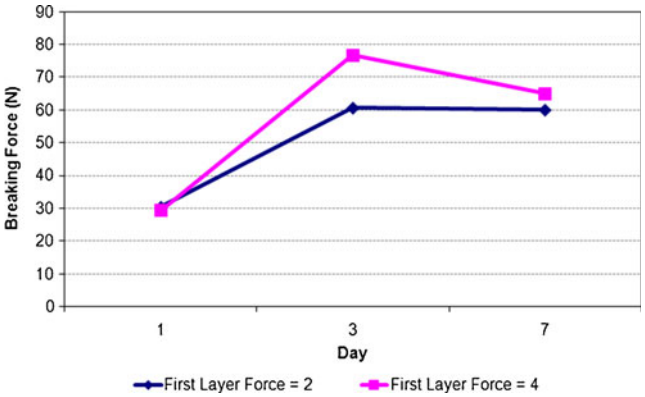

Fig. 16. Effect of first layer force and storage time at low compaction speed on the strength of bilayer tablets

Tablet strength of the Avicel–lactose (Fig. 13) and lactose–Avicel (Fig. 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 (Fig. 15) tablets show an increasing trend in the strength from days1 to 3 with little change from days 3 to 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.

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

Strength of the tablets increases from days1 to 3 and levels off from days3 to 7 for both compaction speeds (Figs. 16 and 17). There is no effect of first layer compression force on day1 for either compaction speeds. At day3, tablet strength increases with higher first layer compression force for the high compaction speed (Fig. 17) but there is no difference at the low compaction speed (Fig. 16). From days3 to 7, the tablet strength decreases slightly for the high first layer compression force but remains flat for the low first layer compression force.

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 paper 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

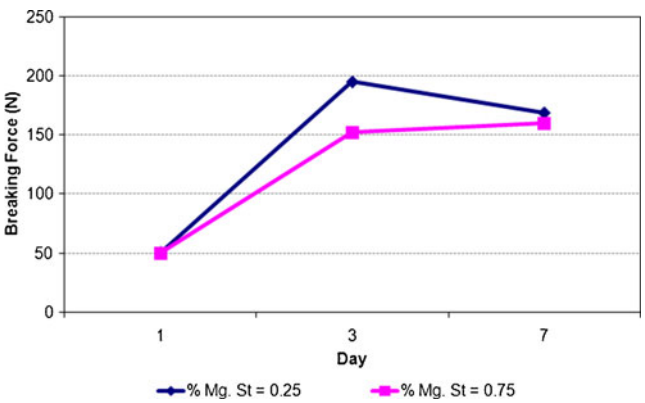

Fig. 15. Effect of lubricant conc. and storage time on the strength of Lactose-Lactose bilayer tablets

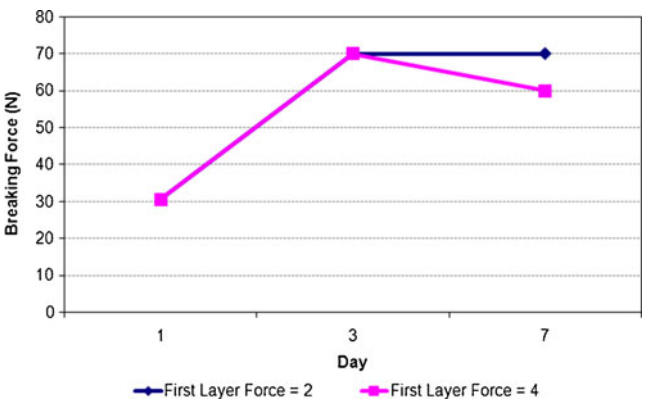

Fig. 17. Effect of first layer force and storage time at high compaction speed on the strength of bilayer tablets

was observed. There is a strong interaction between the first layer compression force and compaction speed for the lactose–lactose tablets.

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