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Evaluation of Bilayer Tablet Machines—A Case Study

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ABSTRACT

Four bilayer tablet compression machines were evaluated for their suitability for compression of a specific bilayer tablet formulation. Tablet machines evaluated were: Manesty (Model No. BB4), Manesty (Model No. Rotappress), Fette (Model No. P3102) and Kilian (Model No. 51AST-ZS) tablet presses. The tablet delamination tendency was the primary acceptance criteria for the evaluation of tablet press performance. The compression force on layer I was found to be the major factor influencing tablet delamination. It was found that the Kilian press was best suited for the compression of the model bilayer tablet formulation. The Kilian press is equipped with a special sampling device for layer I which allows additional compression force to be applied on layer I only at the time of weight sampling. The sampling device then returns to the original set points after sampling is completed. This feature maintains the compression force on layer I to a minimum

during routine compression. Data indicated that the compression force on layer I and the compression zone in the die cavity of layer II were two factors needing to be controlled in order to yield bilayer tablets with acceptable physical characteristics.

INTRODUCTION

The development of instrumented tablet presses during the past 30 years has yielded important information about the compression behavior of tableting materials (1, 2). Measurement of upper and lower compression forces, ejection forces and die-wall forces has been useful in providing a powerful aid in the design and study of formulations (3, 4). However, the extensive knowledge base was primarily built on the single layer tablet formulation. In a review of the literature, information concerning the compression characteristics of a bilayer tablet formulation is rarely mentioned. The bilayer dosage forms are usually prepared for two reasons : to separate, physically or chemically, incompatible ingredients; or to produce repeat-action or modified release products. With the recent advance in design of the bilayer tablet machine, such as the automatic in-process monitoring system, a good opportunity is provided for scientists to better understand the compression characteristics of the bilayer tablet formulation. This article describes the results of a study of a model bilayer tablet formulation using four bilayer tablet presses. The parameters measured were compression force, friability and layer cohesion (e.g. delamination tendency). The objective was to compare and evaluate the suitability of four bilayer tablet presses for the compression of this model bilayer tablet formulation. In addition, the critical tablet press parameters which would affect the formation of the bilayer tablet were studied.

EXPERIMENTAL

MATERIALS AND METHODS

A model bilayer tablet formulation containing two different layers of granulation was utilized as the model formula for the compression studies. The first layer was an antacid granulation and the second layer was an aspirin

granulation. Tablets containing 690 mg of either an antacid or an aspirin granulation were compressed with four levels of compression force using a Betapress to establish compressibility profiles of the individual layers. Compression speed of 800 tablets per minute was utilized for the study. Bilayer tablets were compressed using 306 mg (44.3 % w/w) of antacid granulation and 384 mg (55.6 % w/w) of aspirin granulation using the appropriate tablet press. In general, the antacid layer was fed as layer I and the aspirin layer was fed as layer II feed frames. Layer weights were adjusted by weight adjustments of layer I and layer II. Compression speed of the presses ranged from 1500 to 1750 tablets per minute. Compression trials were conducted for a period of 40 to 120 minutes, depending on the batch size.

TABLETING EQUIPMENT

An instrumented Manesty Betapress equipped with four sets of 7/16" round, shallow, concave, plain punches (0.028" cup depth) was used for the compression of the single layer tablet. The four bilayer tablet presses that were utilized for the compression of the bilayer tablets included: Manesty BB4 - 27 stations (Thomas Engineering, Hoffman Estates, IL); Manesty Rotappress - 45 stations (Thomas Engineering, Hoffman Estates, IL); Fette tablet press (Model No. P3102) - 45 stations (Fette America, Rockaway, NJ); and Kilian tablet press (Model No. RX51AST-ZS) - 51 stations (Kilian & Co., Horsham, PA). The 7/16" round, shallow, concave, plain punches were utilized for the studies.

TESTING

An Inppec tablet tester (Model # HT-TMB 35C, Vector Corp., Marion, IW) was used to measure tablet weight and hardness. Vanderkamp tester (Model # 10809, Vankel Industries, Edison, NJ) was used to measure the friability and delamination of the tablets. An extended friability test (e.g. 500 revolutions in 20 minutes) was employed to determine the delamination and capping tendencies of the tablets. The acceptance criterion was that all tablets should not be delaminated or capped following the extended friability test.

RESULTS AND DISCUSSION

Bonding Mechanisms

The formation of a compact from a powder can be subdivided into the following stages: particle rearrangement; elastic deformation of particles; plastic deformation of particles; fragmentation of particles; and formation of interparticulate bonds. If these volume reduction mechanisms are to result in a permanent consolidation into a compact, then bonds must be formed between solid surfaces in the compact. The dominating bond types adhering particles together in compression of dry powders could be limited to three types: (a) solid bridges formed by a melting process; (b) distance attraction forces, such as intermolecular forces; and (c) mechanical interlocking between irregularly shaped particles. The first type of bonding corresponds to strong bonds, where a true area of contact is established between adjacent particles. The second group could be described as weaker bonds acting over distances. Intermolecular forces constitute the dominating bonding mechanism for pharmaceutical materials. A prerequisite for the formation of a coherent compact is that the surfaces should deform to such an extent that the combined effects of bonding with intermolecular forces and solid bridges are greater than the elastic component of the material. This can be described as the critical compaction pressure needed to form a compact (5, 6).

The effective amount of surface area available for bonding is dependent on several material properties. The following material properties favor a high compact strength: (a) limited elastic deformation; (b) high compact surface area as a result of either fine particulate starting materials or highly fragemented starting materials or starting materials possessing high surface roughness; and (c) extreme plastic deformation (e.g. such as amorphous binders). Both the particle characteristics of the starting material and the changes caused by the volume reduction will be determining factors of the compact strength. An increased particle fragmentation can increase compact strength, owing to a greater bonding surface area. A decrease in particle size and an increase in particle surface roughness can result in stronger compacts. The final compact strength is a

complex function of many material properties, inter-particle size and shape of the starting material, volume reduction behavior and the dominating bond mechanism (5, 6).

It should be pointed out that the ability to obtain and adjust for the correct weight of an individual layer is the most critical and desired feature for bilayer tablet presses. The ability to monitor layer weight during the compression run is critical in assuring content uniformity of the final product. By knowing the exact weight of the first layer of granulation, the weight of the second layer of granulation can be calculated by subtracting the weight of the first layer from the total weight of the tablet. There are two ways the layers are removed for weight and hardness checking. In the first method, the first layer or the two separate layers are diverted from the machine (e.g. such as for the Kilian and Fette tablet presses); in the second method, the first layer is made so hard that the second layer will not bond to it or will bond only weakly, therefore, upon ejection of the completed tablet, the layer may be easily separated by light agitation of tablets and tested individually (e.g. such as for Manesty BB4 tablet press) (7).

Evaluation of Bilayer Tablet Machines

The four bilayer tablet machines evaluated in this study are routinely used to manufacture commercial scale bilayer antacid chewable tablets. The resultant antacid tablets remained intact and did not show delamination throughout their entire shelf life. Data indicated that these four bilayer tablet machines can be used to manufacture bilayer tablets with materials composed of good compressibility and bonding capacity. Since the granulation layers utilized in this study were considered to be materials with marginal compressibility, it offered an opportunity to evaluate the special features of each of these tablet machines in terms of improving the compressibility of this model bilayer tablet formulation.

Tablet press specifications for the four bilayer tablet presses are detailed in Table 1. In terms of special features to enhance the compression process, both the Manesty BB4 press and Manesty Rotappress were considered as simple bilayer presses equipped with adequate basic features to perform routine compression.

Table 1

SPECIFICATIONS FOR FOUR BILAYER TABLET PRESSES

Tablet Press Specifications*				
Tablet Press	Manesty BB4	Manesty Rotappress	Fette P3102	Kilian RX51AST-ZS
No. of stations	27	45	45	51
Output tabs per hr. Maximum Minimum	 162,000 54,000	 259,200 64,800	 486,000 -	 460,000 50,000
Maximum Compaction Force	65kN	65kN	80kN	100kN
Maximum Depth of Fill	17.5mm	17.5mm	18mm	20mm
Maximum Tablet Diameter	16.0mm	16.0mm	16.0mm	16.0mm
Maximum Precompression Force	None	None	20kN	20kN
Upper Punch Entry	1.5mm - 8mm	3.2mm - 6.4mm	2mm - 8mm	1mm - 8mm
Precompression Force Control Layer I Layer II	 No No	 No No	 Yes Yes	 Yes Yes
Approximate Weight	910kg	2286kg	3400kg	2400kg
Height of Machine	1550mm	1702mm	1965mm	1760mm

*Subject to the characteristics of the product.

Both the Fette and Kilian presses were viewed as the more sophisticated bilayer presses equipped with special features. This could provide more in-depth compression information to aid the formulator to better understand and fingerprint each individual formulation. The product output was roughly two times higher for both the Kilian and Fette presses as compared to the Manesty presses. Both Kilian and Fette presses provided a higher compaction force (80-100 kN) as compared to either of the Manesty presses (65kN).

The Kilian and Fette tablet presses were equipped with an automatic in-process monitoring system to provide compression characteristics of the tablets. The main compression force for both layers I and II can be controlled and monitored during the entire compression run to provide detailed compression characteristics of the tablets. On the other hand, neither of the Manesty presses have the monitoring system to provide the compression force information. For the Kilian and Fette presses, both the layer I and layer II precompression forces can be controlled separately to allow precise control of the deaeration during die filling, which in turn could minimize the capping tendency. Neither of the Manesty presses have any precompression force control capabilities. In addition, adjustment of the precompression zone and the depth of punch penetration are defined clearly for the Kilian and Fette tablet presses to provide for the exact compression locations in the die. These special features allow the formulator to have the capability to fingerprint each tablet formulation, and to gather the needed information to maximize batch-to-batch reproducibility.

The Kilian press also is equipped with a special layer I sampling device. This sampling device is controlled by a hydraulic cylinder, which is located between the layer I compression station and the layer I sampling station, and can be activated by engaging the clutch during layer I sampling. This step allows an additional compression force to be applied during sampling only to provide a stronger layer I compact without affecting the actual compression force utilized in the compression process. The schematic of the layer I sampling device is given in Figure 1. As an improvement, the new Fette tablet press (Model No. PT3090IC) also is equipped with a similar type of layer I sampling device; however, the Fette press (Model No. P3102) utilized in this study was not equipped with this sampling feature.

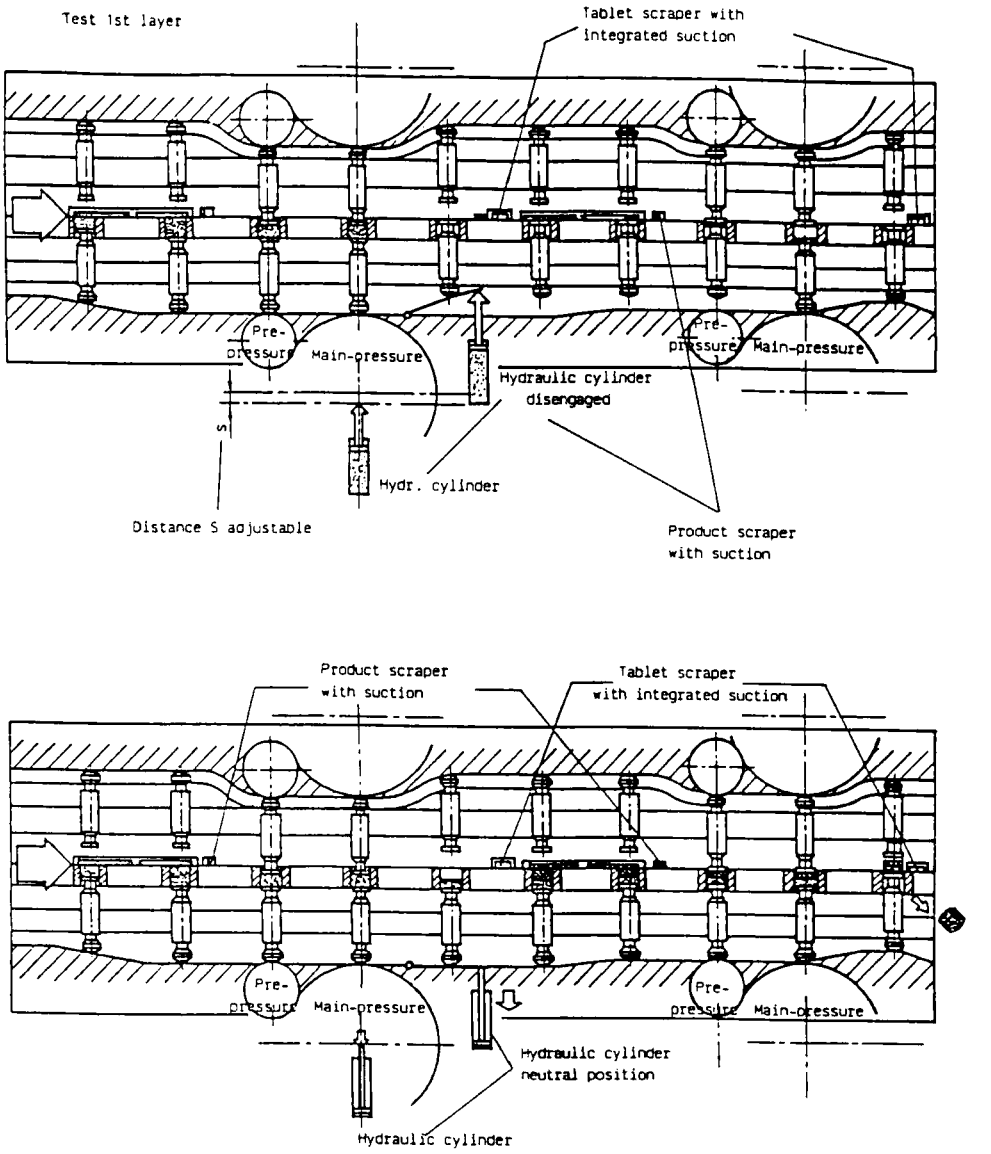

Figure 1. Schematic of a Bilayer Tablet Press During the Sampling of the First Layer (Kilian Press).

Compression Profile of the Single Layer Tablet

The compression profiles of the two single granulation layers are shown in Figures 2 and 3. The data indicated that the antacid granulation exhibited a

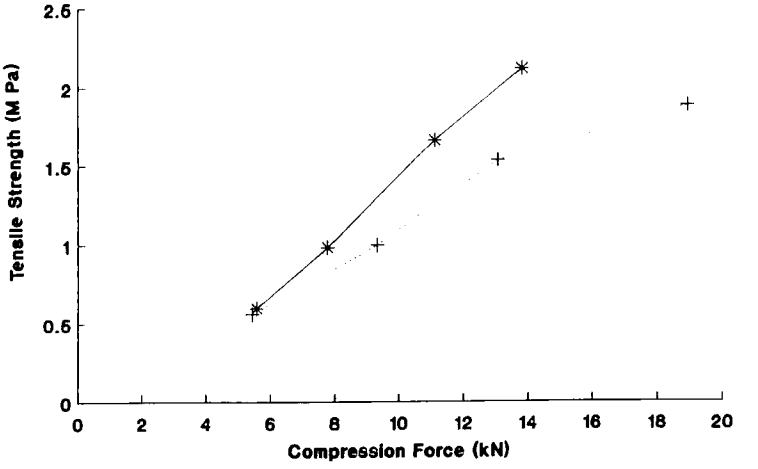

Figure 2. Compression Profiles of Two Different Layers of Granulation ; ✱ - Antacid Granulation; ┼ - Aspirin Granulation.

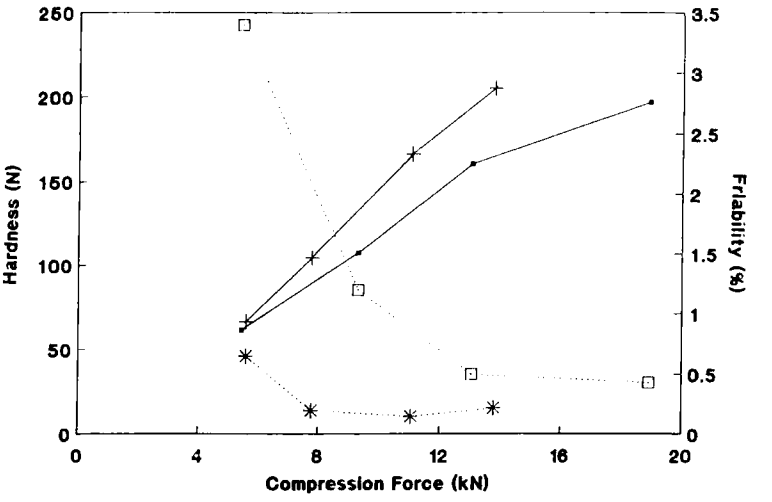

Figure 3. Effect of Compression Force of Two Different Layers of Granulation on the Hardness and Friability of the Resultant Tablets ; ┼ - Antacid (Hardness); ■ - Aspirin (Hardness); ✱ - Antacid (Friability); □ - Aspirin (Friability).

better compression profile than the aspirin layer. The resultant antacid tablets showed a higher tensile strength at a given compression force than the aspirin tablets. The data indicated that the antacid granulation was more elastic and less brittle as compared to the aspirin granulation. The slope of the linear part of the strength-pressure profile (Figure 2) was approximately one and one-half times higher for the antacid granulation than for the aspirin granulation, indicating that the antacid granulation was bonding with a stronger bond type or that the surface area available for bonding was higher. In addition, antacid tablets with acceptable friability (>1.0%) could be obtained using a compression force of 6 kN whereas the aspirin tablets required 11 kN of compression force to attain 1.0% friability. Based on the compression profiles, the antacid layer granulation was fed as layer I because of its higher tensile strength. The weaker aspirin layer granulation was fed as layer II to minimize tablet delamination tendency. In doing so, the aspirin granulation could only be compressed once by the final compression force, which in turn, would provide the optimum cohesion of the layers with the antacid granulation.

Effect of Compression Force of Layer I on the Physical Properties of the Bilayer Tablet

Delamination is defined as the separation of a bilayer tablet into two distinct layers. That is, the separation of the first layer from the second layer. The cause of the phenomenon was attributed to the deformational properties of the formulation during and immediately following compression (8). It was found that the compression force of layer I was a critical factor affecting the propensity for tablet delamination. Any excess compression force on layer I would lead to tablet delamination during the initial testing regardless of the type of tablet machine used for the compression. The Manesty BB4 press, Manesty Rotappress and Fette Press could not be used for the compression of this bilayer tablet formulation due to tablet delamination tendencies observed during the initial friability testing. The primary cause of this delamination tendency was identified to be the higher compression force required on layer I sampling for these three tablet presses at the time of layer I weight adjustments. The ability to monitor layer I weight during the

compression run is critical in montoring and assuring content uniformity of the final bilayer tablet. The only way to compress this model bilayer tablet formulation with acceptable tablet delamination using these three tablet presses was to minimize layer I compression force to a level that did not allow sampling of layer I (e.g. the sample came out as a loose powder compact and could not be accurately weighed) during normal routine compression runs.

The Kilian tablet press was best suited for the compression of this model bilayer tablet. This press was equipped with a special sampling device for layer I which allowed an additional compression force to be applied on layer I only at the time of weight check. It then returned to the original set points of compression force after the completion of sampling. This feature maintained the compression force on layer I to a minimum during routine compression. The effect of compression force of layer I on tablet delamination using the Kilian press is shown in Table 2. It can be seen that when the compression force used for the compression of layer I was decreased (by increasing the tablet thickness from 2.5 mm to 3.5 mm), tablets with acceptable delamination tendency were obtained (Experiment No. 3).

The possible explanation for the above observations can be attributed to the basic compression characteristics of the materials (9, 10, 11). As reported in the literature (8), layer tablets usually undergo a light compression as each component is laid down, with the main compression being the last one. The slug (layer I) should be compressed as soft as possible during the initial compression. The function of the layer I compression force is to tamp the material to make room in the die for the second layer of material. To produce adequate bonding to surrounding materials, plastic deformation of material at the boundary is necessary. Ideally, much deformation should occur in the slug material during the second compression. This will produce greater areas of contact at the interface and thicken the transition region, that is, it will not be confined to the surface that was previously in contact with the punch. The greater the change of volume of the slug when the final compression is made, the better the probability that the bond at the interface will be strong. Furthermore, the radii of curvature of the surfaces in contact is increased by plastic deformation of these surfaces. The area available for adhersion increases as the radii of curvature is increased, hence more bonded

Table 2

KILIAN TABLET PRESS SETTING PARAMETERS FOR THE COMPRESSION TRIALS OF BILAYER TABLETS: EFFECT OF COMPRESSION FORCE ON LAYER I ON TABLET DELAMINATION

Experiment #	Layer I		Layer II		
	Tablet Thickness (mm) [Comp. force adj]	Main Pressure Roller Setting (mm) [Comp. zone adj] (1–8 mm)	Tablet Thickness (mm) [Comp. force adj]	Main Pressure Roller Setting (mm) [Comp. zone adj.] (1–8 mm)	Delamination Tendency
1	2.5	6.6	2.8	1.55	Not Acceptable
2	3.0	6.6	2.8	1.55	Not Acceptable
3	3.5	6.6	2.8	1.55	Acceptable

NOTE:

NO PRE-COMPRESSION FORCE WAS USED FOR THE COMPRESSION

areas may exist. A large volume change is expected in order to accomplish both an increase in radii of curvature and an increase in the number of interparticle contact points in the interfacial "cross section". The final compression puts both layers under nearly the same compression stress. Thus, the maximum change in solid fraction in the slug during the final compression is a desired condition (12).

In addition, the types of binders utilized for the preparation of the single layer granulation may also play a critical role in affecting the compression profile of the resultant tablets. As reported by Karehill el. al., (5) the physical characteristics of tableting compounds can affect the formation of multilayer tablets. For materials undergoing volume reduction, mainly by plastic deformation (materials consolidating mainly by plastic deformation), a decrease in surface roughness of the first layer of the bilayer tablet, obtained by an increase in compaction load, results in a marked decrease in interparticulate attraction between the two layers. This is found for Avicel PH 101 and pregelatinized starch, which bind solely with intermolecular forces. Both materials fail in the contact zone between the first and the second layer of the double layer tablet, indicating that the bonding strength in the contact zone generally is lower than in the individual layers. On the other hand, for easily fragmenting materials, such as lactose and sucrose, the pretreatment of the first layer does not significantly influence these attractions. Thus volume reduction by fragmentation seems to be a more efficient means of producing larger surface areas that will promote interparticulate attraction in the compacts. It is suggested that high fragmentation of tableting compounds and excipients will facilitate the formation of mechanically strong bilayer tablets.

As can be seen from Table 3, the binders utilized in the preparation for the antacid and aspirin layer granulations were mainly Avicel PH-101 and pregelatinized starch. It was found in the preliminary prototype formulation development work that the amount of Avicel PH101 and instant corn starch in the antacid granulation was critical to ensure the bonding between the two layers. Since these binders were materials consolidating mainly by plastic deformation, an increase in compaction load of these two materials led to a decrease in interparticulate attraction between the two layers of the bilayer tablet. Therefore, bilayer tablets, which were compressed by higher compression forces in layer I ,

Table 3

COMPOSITION OF BINDERS USED IN THE TWO INDIVIDUAL LAYER GRANULATIONS

	Antacid Granulation (Layer I)	Aspirin Granulation (Layer II)
Binder Used for Granulation Process (Inter-binder)	Instant Corn Starch (3.3% w/w*)	Pregelatinized Starch (9.4% w/w*)
Binders Used as a Dry Add in the Layer Blend (Intra-Blinder)	Instant Corn Starch (2.0% w/w*)	———
	Avicel PH 101 (2.9% w/w*)	Avicel PH 101 (3.9% w/w*)

* - % w/w expressed as the weight of the individual layer granulation.

delaminated (Experiment No.1 and No.2 in Table 2). The high compression force in layer I reduced the surface roughness of the material, which in turn produced a smaller bonding surface area and hence weaker compacts. The irregular Avicel particles, which bonds by mechanical interlocking, could, by extensive high compression force of the first layer loose all the potential for locking or shape related interactions between the particles. Subsequently, this led to a diminishing of the intermolecular force for bonding of the two layers. As the compression force in layer I was reduced to provide only a tamping effect to the granulation, the reduction of the surface roughness of the layer material would be minimized, which in turn preserved the bonding surface area for strong bonding. The resultant bilayer tablets did not show delamination (Experiment No.3 in Table 2). The compression force utilized for the compression of this bilayer tablet supported this observation. The compression force of layer I utilized for the compression was only 1.2 kN (4.3% of the total compression force), whereas a substantially higher layer II compression force was applied (26.8 kN; equivalent to 95.7% of the total compression force) to yield the bilayer tablets with acceptable delamination.

Effect of Compression Zone in the Die Cavity on the Tablet Capping Tendency

Capping of tablets was observed during the compression of the bilayer tablets using the Kilian tablet press. Capping refers to the tablet when its top is cracked at the edge or is loose as a cap. Three major reasons for the occurrence of capping are as follows: insufficient binder, moisture, or cohesive forces among granules; excessive pressure during compression; and air entrapment (12, 13). Capping, as a result of entrapment of air among granules which is unable to escape during compression, can be eliminated either by the use of precompression force (8, 9) or by controlling the compression zone in the die cavity (8). The use of precompression force allows the precompressed compact time to undergo some stress relaxation before the final compression force is applied. This stress relaxation time can reduce the capping tendency (12). By regulating the depth of penetration of the upper punch, the compression may be performed over some range of locations within the die to reduce capping tendency (8). As the first measure, the use of precompression force on the Kilian tablet press on either layer I or layer II was utilized to minimize the capping tendency of the resultant bilayer tablets. However, the data indicated that the use of precompression force did not improve tablet capping of this model bilayer tablet formulation but increased the potential of tablet delamination. As discussed previously, use of additional force on layer I compression led to the tablet delamination of this bilayer tablet. The use of precompression force represented an additional compression step for the layer I material in addition to the two main compression steps. This additional compression step, even though it required a relatively low compression force, would still reduce the surface roughness of the material and subsequently lead to a decrease in the interparticule attraction between the two layers. This would lead to a higher propensity for tablet delamination.

It was found that the capping tendency of these bilayer tablets could be minimized by manipulating the setting of the compression zone in the die cavity of layer II. Depending on the compression zone setting, different levels of capping tendency were observed (Table 4 and Figure 4). By raising the compression zone of layer II from 2.6 mm to 1.5 mm from the top of the die cavity, the resultant

Table 4

KILIAN TABLET PRESS SETTING PARAMETERS FOR THE COMPRESSION TRIALS OF BILAYER TABLETS: EFFECT OF DIE-CAVITY COMPRESSION ZONE (LAYER II) ON CAPPING TENDENCY

Experiment #	Layer I		Layer II		
	Tablet Thickness (mm) [Comp. force adj]	Main Pressure Roller Setting (mm) [Comp. zone adj] (1-8 mm)	Tablet Thickness (mm) [Comp. force adj]	Main Pressure Roller Setting (mm) [Comp. zone adj.] (1-8 mm)	Capping Tendency
4	2.7	6.5	3.6	2.6	Not Acceptable
5	2.7	6.5	2.8	2.0	Not Acceptable
6	2.7	6.5	2.5	1.5	Acceptable

NOTE:

NO PRE-COMPRESSION FORCE WAS USED FOR THE COMPRESSION

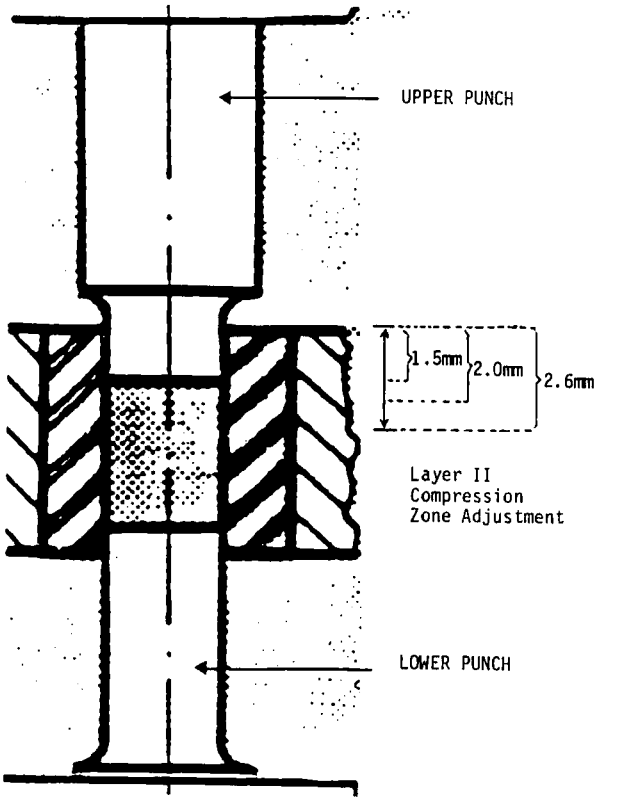

Figure 4. Locations of Compression Zone in the Die Cavity of Layer II.

tablets displayed minimum capping tendency. Compressing the granulation at the upper location in the die cavity might reduce air entrapment during compression and minimize tablet capping of the resultant bilayer tablets.

CONCLUSION

Data from this study indicated that the compression force on layer I was the major factor affecting bilayer tablet delamination and the compression zone in the die cavity of layer II was the critical factor controlling tablet capping tendencies. The practice of using precompression force to reduce tablet capping should be used cautiously when dealing with the bilayer tablet formulation

Table 5

KILIAN TABLET PRESS SETTING PARAMETERS FOR THE COMPRESSION TRIALS OF BILAYER TABLETS: EFFECT OF COMPRESSSION FORCE (LAYER I) AND COMPRESSION ZONE (LAYER II) ON TABLET CHARACTERISTICS

Experiment #	Layer I		Layer II			
	Tablet Thickness (mm) [Comp. force adj]	Main Pressure Roller Setting (mm) [Comp. zone adj] (1-8 mm)	Tablet Thickness (mm) [Comp. force adj]	Main Pressure Roller Setting (mm) [Comp. zone adj.] (1-8 mm)	Tablet Delamination Tendency	Tablet Capping Tendency
7	3.5	6.5	4.0	2.5	Acceptable	Not Acceptable
8	3.5	6.6	2.9	1.55	Acceptable	Acceptable

NOTE:

NO PRE-COMPRESSION FORCE WAS USED FOR THE COMPRESSION

consisting of materials of poor compressibility. Both compression force on layer I and compression zone in the die cavity of layer II were interrelated factors that must be controlled to yield bilayer tablets with acceptable physical characteristics (Table 5). Furthermore, the data implied that one should use the new bilayer tablet press whenever possible to evaluate bilayer tablet formulations. These new tablet presses are equipped with the computer monitoring capability to provide the essential compression characteristics or profiles to fingerprint the bilayer tablet formulation. The layer I sampling apparatus on the Kilian tablet press (or a similar sampling device in other bilayer tablet presses) was found as one of the important features for bilayer tablet presses to allow the needed flexibility to control the formation of the bilayer tablets.

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