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Review

Review of bilayer tablet technology

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ABSTRACT

Therapeutic strategies based on oral delivery of bilayer (and multilayer) tablets are gaining more acceptance among brand and generic products due to a confluence of factors including advanced delivery strategies, patient compliance and combination therapy. Successful manufacturing of these ever more complex systems needs to overcome a series of challenges from formulation design to tablet press monitoring and control. This article provides an overview of the state-of-the-art of bilayer tablet technology, highlighting the main benefits of this type of oral dosage forms while providing a description of current challenges and advances toward improving manufacturing practices and product quality. Several aspects relevant to bilayer tablet manufacturing are addressed including material properties, lubrication, layer ordering, layer thickness, layer weight control, as well as first and final compression forces. A section is also devoted to bilayer tablet characterization that present additional complexities associated with interfaces between layers. The available features of the manufacturing equipment for bilayer tablet production are also described indicating the different strategies for sensing and controls offered by bilayer tablet press manufacturers. Finally, a roadmap for bilayer tablet manufacturing is advanced as a guideline to formulation design and selection of process parameters and equipment.

Contents

1. Introduction

Solid oral dosage forms are the preferred route for many drugs and are still the most widely used formulations for new and existing complex-configuration dosage forms such as controlled-release (Conte et al., 1993; Nangia et al., 1995; Chidambaram et al., 1998; Abdul and Poddar, 2004), osmotic pumps (Wong et al., 2002), and compression-coated tablets (i.e., tablet within a tablet) (Shivanand and Sprockel, 1998; Zerbe and Krumme, 2002; Ozeki et al., 2004). The controlled-drug delivery systems typically require more demanding mechanical testing, characterization, and monitoring techniques with faster response times than

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those possible with traditional measurement approaches (Mashadi and Newton, 1987; York et al., 1990; Hancock et al., 2000). In recent years, pharmaceutical drug product manufacturers have oriented their product development activities to fixed dose combinations (FDCs) for treatments like type 2 diabetes, hypertension, pain and HIV/AIDS to mention a few. Several different approaches are employed to deliver the FDC products to the patients such as multilayer tablets (Benkerrour et al., 2004), compression coating, active coating (Desai et al., 2013; Charlton and Nicholson, 2010), bilayer floating tablet (Ranade et al., 2012; Lalita et al., 2013) and buccal/mucoadhesive delivery systems (Park and Munday, 2002; Yedurkar et al., 2012). Among these approaches, the multilayer tablets drug delivery is gaining popularity and particularly the bilayer technology has attracted manufacturers' attention for the development of products for life cycle management (LCM).

If bilayer tablets are inadequately manufactured, the tablets could split apart leading to a very critical defect since it could potentially result in a patient not receiving one of the intended drug component. The residual stress distribution in the tablet is suspected to be a major cause of the resultant tablet inhomogeneity causing the tablet to fracture and split apart (Inman et al., 2007). The fracture of multilayered tablets is often the result of an interfacial crack driven by residual stresses in the tablet and propagating a finite distance within the tablet. This leads to capping and lamination, which may not always be immediately apparent after compaction (Hiestand et al., 1977; Abdul and Poddar, 2004; Inman et al., 2007). It is known that occurrence of the fracture/crack at the interface causes a reduction in the overall elastic stiffness (Young's modulus) and layered tablets become fragile and develop a tendency to fail. Therefore, while the therapeutic (chemical/pharmaceutical) functions of multilayered tablets are crucial, they need to have sufficient mechanical strength and ruggedness to survive normal processing, handling, packaging, and shipping stresses. Understanding what influences the stress state and mechanical properties of a multilayered tablet and developing specialized techniques for measuring those properties will assist in the understanding of how, and why, defects such as capping, delamination, and cracking occur. According to Wu and Seville (2009), understanding and predicting the mechanical strength of bilayer tablets is of commercial significance since bilayer tablet failures (delamination) due to weak mechanical strength can lead to enormous financial loses.

This review mainly focuses on the advantages and the main challenges associated with bilayer compaction technology including impact of material mechanical properties, characterization techniques for interface between layers, compression parameters, as well as features offered by commercial bilayer compression machines.

2. Key advantages of bilayer tablets

Several advantages of the bilayer technology were reported in the literature. The main ones are listed below.

- Two chemically incompatible active pharmaceutical ingredients (APIs) can be formulated in a bilayer configuration. In some cases, depending on the magnitude of the incompatibility between the two APIs, an intermediate layer needs to be added to provide physical separation between the two layers (Li et al., 1995; Benkerrour et al., 2004; Efentakis and Peponaki, 2008; Vaithiyalingam and Sayeed, 2010).
- Two APIs or the same API with different release profiles can be delivered as a single bilayer tablet (e.g. drugs with an extended release and an immediate release profiles) (Zerbe and Krumme, 2002; Nirmal et al., 2008; Shiyani et al., 2008).
- Combining two or more APIs in a single bilayer tablet reduces the dosing unit burden thereby improving patient compliance (La Force et al., 2008; Charman and Charman, 2002; Bangalore et al., 2007).
- As most bilayer tablets are developed as part of a Life Cycle Management program, the bilayer technology provides possibility of prolonging patent life of a drug product (Veroma and Garg, 2001; Abebe et al., 2010).
- Increased efficacy of the active components due to their synergistic effect (Serebruany et al., 2004; Benkerrour et al., 2004).

3. Challenges related to bilayer technology

In spite of the aforementioned advantages provided by the bilayer technology, several issues associated with the mechanisms and compression of bilayer tablets have been reported in the literature in recent years. The formulators and process scientists need to overcome the challenges to deliver a robust bilayer tablet and manufacturing process. Some of the key challenges are:

- Inaccurate individual layer weight control (Charman and Charman, 2002).
- Cross contamination between the layers (Hiestand et al., 1977; Karehill et al., 1990; Poon and Bhushan, 1995; Inman et al., 2007; Akseli et al., 2013).
- Elastic modulus mismatch between the adjacent layers. High elastic modulus ratio between adjacent layers could cause insufficient layer bonding and relatively low interfacial strength (Akseli et al., 2010).
- Reduced production yield and the propensity to delaminate (distinct layers separation) at the non-planer interface between the adjacent compacted layers (Abdul and Poddar, 2004).
- Disproportionate layers weight ratio coupled with low drug load (Martin et al., 2012).
- Insufficient bilayer tablet hardness (Abdul and Poddar, 2004).
- Long term physical and chemical integrity throughout shelf life.
- Large tablet size, which can impact the swallowability of the unit dose.
- Impact of high temperature and humidity on layer adhesion upon storage (Kottala et al., 2012a).

Overcoming all these challenges requires a focused effort toward addressing the following areas related to material properties and bilayer processing parameters: (i) determination of mechanical properties of each layer, (ii) maximization of interfacial adhesion between the layers, (iii) optimization of the first layer compression force, (iv) quantification/understanding of factors contributing to delamination, (v) assessment of the impact of layer sequence and layer weight ratio, (vi) development of techniques for small scale material characterization tools that can be applied during bilayer tablet design, and (vii) selection of appropriate bilayer tablet press alternatives with consistent weight control delivering system.

3.1. Material properties

Understanding the fundamental material properties (API and excipients) like brittleness (lactose, di-calcium phosphate), plasticity (microcrystalline cellulose) and visco-elasticity (pre-gelatinized starch) is key in the successful development of bilayer tablets. Depending on the drug load in the formulation, either the API property and/or the excipients property will predominantly impact the compaction property of the formulation.

It has been reported in the pharmaceutical literature that plastically deforming and brittle materials have a significant impact

on the compression process. The compression of a 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 (Wu and Seville, 2009). On the application of a compression force, a brittle material will fracture and fill the voids. In addition, due to differences in the elastic Young's modulus, materials relax at different rates during decompression. Elastic mismatch of the adjacent layers in a bilayer configuration is due to differences in the Young's modulus and deformation histories of the respective individual layers. This generates radial stresses, which in turn causes the bilayer tablets to delaminate. Propagation or transmission of compression force through the materials also changes with the material properties. Eiliazadeh et al. (2004) suggested that a greater particle deformation in the lower central region of the die than at the outer radial regions can be attributed to the applied compression stress, which acts primarily in a downward central direction. This phenomenon is due to the wall friction, which retards the vertical movement of the particles in contact with the die. The expansion of a tablet continued over several days after ejection from a die (elastic recovery), and the amount of expansion was demonstrated to be different depending on the materials evaluated (e.g. microcrystalline cellulose, dicalcium phosphate, hydroxypropyl methyl cellulose) (Picker, 2001). Kottala et al. (2012a,b) concluded that the nature of materials played a critical role on the strength of bilayer compacts and also on their mode of fracture.

Recently, Akseli et al. (2013) suggested that when the first layer was compressed to a low porosity, the bonding with the second layer became difficult and it was impossible to produce intact bilayer tablets composed of microcrystalline cellulose and pregelatinized starch. This implies that the strength (σ) of the layer was greater than the strength of the interface ($\sigma_{layer} > \sigma_{interface}$). For bilayer tablets (MCC in the first and second layers and tablet diameter of 10 mm) compacted with initial forces of 2 kN and 4 kN, the authors observed that once the second layer compression force reached 18 kN, tablets failed in the first layer rather than in the interface ($\sigma_{layer} < \sigma_{interface}$), indicating a change in the mode of failure from the inter-layer ($\sigma_{interface}$) to the intra-layer (σ_{layer}) mode. This is in agreement with the findings reported by Lacombe (2006). On the other hand, bilayer tablets composed of MCC in the first layer/starch in the second layer, it was impossible to form intact tablets with a final compression force of 6 kN irrespective of the first layer compression forces. These tablets were split apart along the interface either during the decompression-ejection phase or during post-compaction handling due to weak bonding between the adjacent layers. The outcome of the study helped to establish four different fracture patterns namely: clear-layer break, cap-shape break, half-half break and interface break. This demonstrates how material properties strongly impact the strength of the interface and the individual layers, and also the mode of breakage.

In addition, Kottala et al. (2012a) also attempted to understand the impact of different material properties on the strength of bilayer tablets. It was demonstrated that bilayer tablets prepared with brittle/brittle material (lactose/lactose) in both layers exhibited stronger interfacial strength compared to other material combinations (e.g. brittle/plastic or plastic/brittle or plastic/plastic). In other words, the bonding strength between the two layers was higher than that of the individual layers. Furthermore, if brittle materials are present in both layers, the elastic mismatch between the adjacent layers will be minimal as the mechanism of consolidation of brittle material is by fragmentation. Moreover, the interfacial strength was weakest for compacts made with plastic material (MCC) in both layers and tablets delaminated coming off the tablet press.

The surface roughness of MCC in the first layer was reduced significantly for first layer forces varying between 2 and 4 kN resulting in a decrease in inter-particulate attraction and mechanical interlocking between the two adjacent layers. The findings were in agreement with those observed for bilayer compacts prepared with MCC and pre-gelatinized starch (Akseli et al., 2013). Inman et al. (2007) pointed out that due to the rigid nature of the brittle materials, deformability capacity of the particles (higher Young's modulus compared to plastic materials) on the initial layer is significantly reduced and thereby there is substantial roughness still retained on the surface to provide nesting sites for mechanical interlocking. It was also demonstrated that for plastically deforming materials such as MCC and sodium chloride, bonding strengths between adjacent layers decreased with the decrease of interfacial surface roughness (Karehill et al., 1990). On the other hand, 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.

3.2. Compression forces

As reported in the literature (Li et al., 1995; Inman et al., 2007), compression forces applied on the first layer and the second layer significantly impact the interfacial strength and the adhesion between the adjacent layers thereby contributing to the mechanical integrity of the resultant bilayer tablet. To address this major concern, the compression force requires very close attention. The delamination of bilayer tablets is due to the development of various mechanical stresses during compression and particularly during the unloading phase and tablet ejection (Anuar and Briscoe, 2010). Podczeck and Al-Muti (2010) reported that if the material forming the first layer of a bilayer tablet was more elastic, the tension introduced into the system weakened the strength of the bilayer tablets. It has been revealed that the way in which failure of a rectangular beam (bilayer tablet) crossed the interface between different layers was an important factor in determining the tensile strength of bilayer tablets (Podczeck et al., 2006). The evaluation of Li et al. (1995) demonstrated that the compression of the first layer was the most critical factor, which affected layer adhesion. The extent of compact densification and resistance to compressibility within the die cavity was impacted by compaction pressure and the punch velocity. It was demonstrated that an increase in the punch velocity between 50 and 500 mm/s decreased the porosity reduction on individual layers (Yang et al., 1997).

A decrease in axial tensile strength of bilayer tablets observed with increasing first layer compression force for several mechanically different materials, e.g. plastically deforming materials and brittle fragmenting materials, was attributed to the reduction of bonding surface area and adhesion between the layers (Karehill et al., 1990). It was suggested that stresses caused from compaction and elastic material mismatch between layers can result in tablet delamination (Podczeck, 2011). In addition, a fracture toughness test was utilized to examine the fracture behavior of the bilayer interface.

The interfacial strength of bilayer tablets composed of plastic material (MCC in first and second layers) decreased with the increase of the first layer force while maintaining constant the second layer force (Kottala et al., 2012b). To further strengthen the criticality of compression forces in a bilayer configuration, the authors suggested that the bilayer tablets with a diameter of 9.5 mm compressed with first layer force of 0.25 kN fractured in the second layer (though very close to the interface), while tablets prepared with 0.5 and 1 kN first layer compression forces, the bilayer tablets fractured along the interface. On the other hand, bilayer tablets compressed using MCC in first and second layers at a constant first layer force of 2 kN and varying (15–25 kN) second layer force led to an increase in the interface with an increase of the second layer force. These findings support that the interfacial strength

of bilayer tablets made of plastic material is a function of both the applied first and second layer forces. The magnitude of the layer forces governs the degree of deformation endured by the particle assembly. This phenomenon was 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. The level of first layer compression force is critical to determine the degree of surface roughness of the first layer, which is determinant for the interfacial strength of the two layers. The elastic mismatch 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 (Inman et al., 2007). 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 compact will fracture and a crack will form.

As for tablets composed of plastic material (MCC in both first and second layers), the strength of brittle bilayer tablets decreased with the increase of the first layer force (Kottala et al., 2012b). However, unlike bilayer tablets composed of plastic materials, brittle based bilayer tablets did not exhibit any delamination even at a relatively higher first layer compression force of 6 kN. It was also remarked a difference in the mode of breakage between these two materials. In the case of tablets made with brittle material, fracture has occurred in the first layer indicating that interfacial strength is greater than the individual layer strength. As mentioned earlier, breakage has occurred along the interface for bilayer tablets made of plastic materials indicating that layer(s) strength is higher than interfacial strength. Akseli et al. (2013) has also shown that if interfacial strength is weaker than layer strength, then fracture occurs at the interface and vice versa. Earlier, Karehill et al. (1990) 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. As a result, it is preferable to select brittle excipients, which potentially can lead to a sufficient interfacial strength of the bilayer tablet to withstand mechanical shock during its production, packaging and shipping.

3.3. Lubricant

Miller and York (1988) remarked that increased lubricity of a powder blend will reduce the friction between the powder particles that contact with each other or with dies and punches during compression because the lubricant will be distributed uniformly throughout the blend and coat the surface of the particles. In a bilayer configuration, a greater interfacial interaction between the layers can be achieved with low lubricant level for the first layer (Dietrich et al., 2000). The impact of lubricant level when tested (0.25%, 0.5% and 0.75%, w/w magnesium stearate) on tablet strength is more pronounced for plastic materials compared to brittle material (Tye et al., 2005). A study conducted by Kottala et al. (2012a) quantified that the interfacial strength decreased with the increase of magnesium stearate concentration. The tablet surface smoothness increases as the level of lubricant (magnesium stearate) is increased thereby impacting the interfacial interaction between the first and second layers (Sugisawaa et al., 2009). However, the level of lubricant needed for avoiding picking and sticking of the first layer mainly due to the relatively low compression force must be assessed as part of the formulation and process development.

Studies conducted on external lubrication, where lubricant is sprayed onto the dies and punches in lieu of adding directly to bulk granules for each compression cycle, have shown that the external lubrication can increase crushing strength of monolayer tablets by 40% without prolonging the corresponding tablet disintegration (Yamamura et al., 2009). As external lubrication offers advantages for monolayer tablets, it potentially can be applied to assess the impact of lubricant on the quality attributes (interfacial tensile strength and dissolution) of bilayer tablets and this can be of great interest to many researchers.

3.4. Layer ratio and layer sequence

There are a very limited number of publications on the impact of layer ratio and layer sequence in a bilayer configuration on the mechanical strength and other quality attributes of bilayer tablets (Akseli et al., 2013; Kottala et al., 2013). In general, it is a common practice to have a 1:1 or 1:2 weight ratio between the two layers. In most cases, a layer ratio of 1:3, 1:4 can be encountered and even sometimes a disproportionate ratio of up to 1:6 can be evaluated during development. It is more challenging to maintain a consistent second layer weight when the first layer weight is large as compared to the second layer weight (for example, ratio of 1:5 or 1:6). In such circumstances, it is preferred to compress the smaller layer weight in the first layer. However, due to mechanical limitations, the features of the current commercially available bilayer presses do not offer the possibility of compressing the smaller weight in the first layer. Therefore, the formulators have no option than placing the material with a larger weight in the first layer with all its associated challenges (Abebe et al., 2013). In such circumstances, Martin et al. (2012) reported that the upper punch penetration depth during the first layer compression force and during the second layer compression force impacted the potency of the second layer API. It was argued that a deeper upper punch penetration into the die might minimize any sort of splashing out of the second layer material from the die during compression thereby providing potency values close to 100% of label claim. The impact of layer weight ratio on the mechanical strength of the bilayer tablets, which were prepared with MCC and lactose at ratios of 1:3, 1:1 and 3:1 was investigated. There was no significant impact on the breaking force of the bilayer tablets for the materials and ratio ranges studied (Kottala et al., 2013).

To illustrate the impact of layer sequence on the mechanical strength of bilayer tablets, Akseli et al. (2013) prepared bilayer tablets with different layer sequencing subjected to a consolidation process with varying first layer and second layer compression forces, and studied their impacts on the mechanical strength of the resultant bilayer tablets (Fig. 1). When MCC layer compacted first and starch second, the surface roughness of the MCC layer that is in

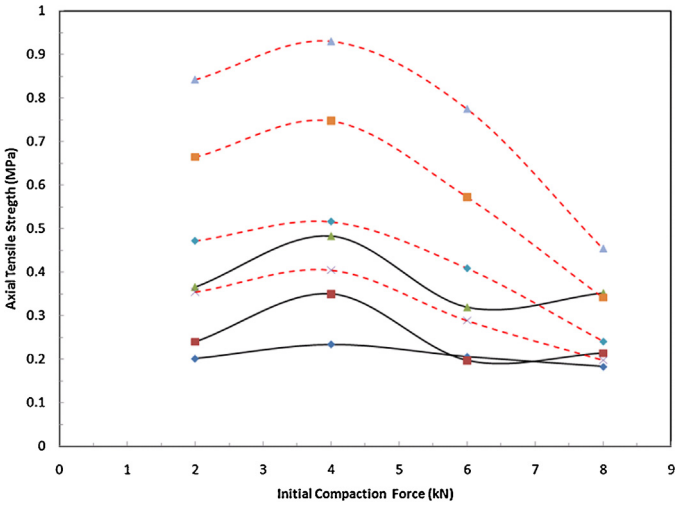

Fig. 1. Comparison of the effect of layer sequence on the axial tensile strength values of MCC–starch (solid lines) and starch–MCC tablets (dashed lines). 6 kN, 10 kN, 14 kN, and 18 kN final compression forces are represented by cross (×) shape, diamond (♦) shape, square (■) shape, and triangular (▲) shape, respectively (Akseli et al., 2013).

Table 1
A summary of layer weight ratio, upper punch penetration and layer sequence impact on bilayer attributes.

Factor	Impact	Reference
Layer weight ratio	• A large weight ratio leads to inconsistent 2nd layer weight (if the 2nd layer is the smaller amount) due to current equipment limitations. • Weight ratio has no impact on tablet mechanical strength	Akseli et al. (2013) and Kottala et al. (2013)
Upper punch penetration	• Shallow penetration promotes splashing out of die leading to reduced potency. • Deeper penetration resolves the challenge	Martin et al. (2012)
Layer sequence	The sequencing of layers with distinct compactability characteristics controls the interface roughness; hence interface strength.	Akseli et al. (2013)

contact with the punch surface significantly reduces (MCC deforms plastically under compression), thus resulting in the decrease in intra-particular attraction between the two different adjacent layers. This can be translated further to the fact that the nesting sites for the starch particles decrease as the surface asperities on the MCC layer decrease and thereby the capacity of bond formation and the possibility of mechanical inter-locking are significantly reduced. However, when starch placed in the first layer and MCC in the second layer, the bilayer tablets exhibited a relatively higher tensile strength values than the MCC–starch tablets. After the first layer compression force, the starch material is not rigid as the MCC material (known to be more compactable than starch) (Tye et al., 2005), and it is considered as a compact made of deformable particles, which have the capacity for further elastic and/or plastic deformation during the compression phase of the MCC layer resulting in a higher tensile strength of the bilayer tablets. A summary of the details provided in this section is listed in Table 1.

3.5. Environmental conditions

The effect of moisture on the strength of bilayer tablets was studied by few authors. Compacts made from hygroscopic materials will respond to the relative humidity of the surrounding air by absorbing/desorbing of moisture into/out of their pore structure (Podczeck, 2012). In addition, if the compacts have been made from, for example, starches, microcrystalline cellulose, crospovidone, hydroxypropyl methylcellulose, polyvinylpyrrolidone, sodium starch glycolate, and colloidal silicon dioxide, moisture can also penetrate the bulk of the particles of these materials. The uptake of moisture into the porous compacts and/or particles leads to layer expansion and to changes in the Young's modulus of elasticity. Any change in layer dimensions will weaken the interface between the layers and might hence contribute to time-dependent delamination (Jones, 1999).

Podczeck and Al-Muti (2010) and Podczeck (2011) extensively studied changes in the Young's modulus of elasticity and their effects on strength and delamination. In general, an increase in moisture results in a decrease in Young's modulus, and very small differences and changes in Young's modulus can lead to ad-hoc delamination. It was recommended that materials should be pre-conditioned to ensure that they are at equilibrium with the moisture of the air in the manufacturing area and the compacts should be packaged into air-tight, moisture protective blisters (Podczeck, 2012). Shen and Springer (1976) described that as thermal diffusion is a rapid process, thermally induced changes in deformation and stresses are usually momentous and can lead to ad-hoc delamination. On the other hand, hygroscopic effects are quite slow (can take anything from days to weeks or even months before moisture equilibrium inside a compact have been achieved) as they depend on the moisture diffusion inside the compact.

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 and dissolution (Kottala et al., 2012a). The strengths of bilayer tablets composed of plastic/brittle, brittle/plastic and brittle/brittle were compared upon storage. For bilayer tablets prepared with MCC in the first layer/lactose in the second, and lactose in the first layer/MCC in the second, the tablet interfacial strength decreased with the increase in humidity and storage time while for those prepared with lactose/lactose, an increase in tablet strength was observed due to the formation of solid bridges upon storage. More recently, Klinzing and Zavaliangos (2013) studied the effect of post production environmental conditions on the interfacial strength of bilayer tablets of MCC/dicalcium phosphate by exposing the tablets to several humidity conditions. It was concluded that transient in moisture diffusion into bilayer tablets with significant differential moisture absorption characteristics are responsible for the reduction of strength in both high and low moisture environments. The authors suggested that the insight gained from their studies will be useful for material selection and packaging of bilayer tablet systems. Further, Zacour et al. (2013) reported that the coating micro-environment experienced by bilayer tablets during pan coating, particularly tablet hardness and coating spray rate, significantly impacts the delamination tendencies of the bilayer tablets under open storage conditions.

3.6. Layer weight control

The materials particle size distribution, flow property and the ability of the bilayer press to accurately control the layer weight are very critical in assuring acceptable content uniformity of the APIs composing the bilayer tablets. Each instrumented bilayer press from different vendors has its own weight control mechanism. The available development and commercial presses offer the possibility of monitoring the first layer weight and the second bilayer weight. To make situations more complex, no commercially available bilayer press is equipped with a device to sample separately the second layer weight. In general, a minimal precompression force is applied on the first layer, which makes sampling more challenging as the tablets do not come of the press solid enough to weigh. Bilayer presses (Kilian, Fette and Korsch) are equipped with a sampling device for first layer compact, which allow applying an additional compression force on the first layer material and thereby hardening the compact and rendering it more suitable for weight check.

3.7. Bilayer tablet characterization

The bilayer tablet formulations used for each individual layer should be compressible (i.e., the ability of a material to undergo a reduction in volume as a result of an applied pressure) and compactable (i.e., the ability of a powdered material to be transformed into tablets with strength during densification) on their own, that

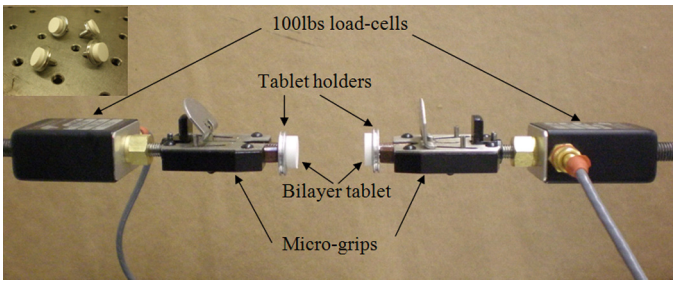

Fig. 2. A close-up image of the bilayer tablet tensile tester equipped with 100 lbs mini-load cells. Inset depicts the examined bilayer tablets glued to the holders (Akseli et al., 2013).

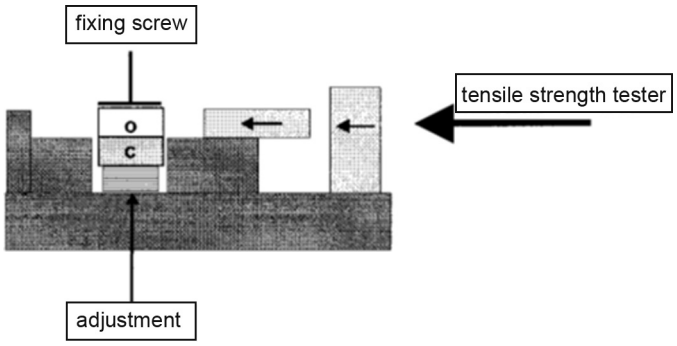

Fig. 3. Shear apparatus for adhesion strength measurements (schematic): c, central-layer tablet; o, outer layer (Dietrich et al., 2000).

is, they should show satisfactory reduction in volume and form mechanically strong and coherent solid bodies. From this point of view, the interface between the layers should weld together during compaction and strong adhesion forces should hold the layers together after tablet ejection. However, this is not always the case, and as compressibility and compactability of the individual layers should not be the cause for delamination, other physical mechanisms need to be identified that can explain the problems with delamination. In the studies published by Karehill et al. (1990), Inman et al. (2007) and Akseli et al. (2013), it was reported that the compression force used to form the first tablet layer should be kept at a minimum to provide sufficient surface roughness for nesting and particle interlocking between layers to occur. Due to the increase in surface roughness, there is a larger contact area between the layers, which enhances interlayer adhesion.

Belda and Melick (2006) used a diametrical compression test to break bilayer tablets composed of pharmaceutical powders. To determine the interfacial strength of bilayer tablets, terahertz pulsed imaging using interface index (Niwa et al., 2013), a flexural test (Busignies et al., 2013) and near infrared transmittance (NIR) spectroscopy (Short et al., 2009; Igne et al., 2011) were applied. NIR was also employed for the control of active pharmaceutical ingredient contents in two separate layers of intact bilayer tablets (Ito et al., 2010). It is highlighted that photoacoustic measurements (Akseli et al., 2008) and ultrasonic techniques (Akseli et al., 2009; Leskinen et al., 2010; Simonaho et al., 2011) have been used to predict the integrity of pharmaceutical compacts. Photoacoustic measurements detect pores and structural faults like cracks inside the tablets (Akseli et al., 2011). A simple predictive model developed by Wu et al. (2006), based on Ryshkewitch–Dukworth equation, has been shown that the model can accurately predict the tensile strength of binary tablets prepared with some commercial excipients. The most current and effective bilayer tablet characterization tools are axial strength test (horizontal or vertical) (Inman et al., 2007; Akseli et al., 2013) (Fig. 2), three-point bending test (Wu and Seville, 2009), shear test for adhesion strength measurements (Fig. 3) (Dietrich et al., 2000), acoustic measurements (in the ultrasonic bandwidth) (Akseli et al., 2010), magnetic resonance imaging (Malaterre et al., 2009), terahertz pulsed imaging (Niwa et al., 2013) and X-ray micro-computed tomography (μCT) (Akseli et al., 2013; Wu and Seville, 2009) (Fig. 4).

Some benefits of bilayer tablet characterization in early formulation development are (i) quantitatively determine the interfacial strength in bilayer tablets, (ii) detect unusual or extreme properties of compacted layers, (iii) ensure lot-to-lot consistency of the resultant tablets, (iv) rationale strategy to guide formulation development and for the selection of compatible product formulations and manufacturing processes, (v) explain material failure mechanisms during tablet manufacturing, (vi) understand the effect of the factors specific to tableting equipment (e.g., speed of operation, applied forces, etc.), (vii) reduction in energy consumption by minimization of faulty tablet production, and (viii) environmental issues and concerns related to the management of waste materials.

3.7.1. 3D characterization tools

X-ray micro-computed tomography is a volumetric imaging technique, which enables non-invasive determination of the density of a material in space on the principle of attenuation of X-rays as it pass through it (Akseli et al., 2013). The specimen is placed on a rotating stage between a micro-focal mono-energetic source and a charge couple detector (CCD) array based detector. A phosphor plate between the specimen and the detector is used to intensify the image. Most modern industrial μCT systems are capable of attaining resolutions of less than 50 μm. Projection images (radiographs) of the object are obtained in slices at specified angular rotational steps; from which horizontal slices are reconstructed utilizing Fourier based Filtered Back Projection (FBP) algorithms. The attenuation values calculated as a function of space obeys the Beer–Lambert's Law (Akseli et al., 2013). Upon normalizing by the mass density, the mass attenuation coefficient is found to be constant for most materials over a range of energies, leaving the attenuation values (CT or HU) as a function of density and path alone. By means of calibration, it is quantitatively possible to determine the density of the sample as a function of space at a sufficiently high resolution. The individual slices can be stacked up and a 3D volumetric reconstruction of the specimen can be obtained using standard interpolation techniques such as marching cubes or adaptive rendering. It was reported by Akseli et al. (2013) that the interfacial cracks between the adjacent layers can be detected (Fig. 4). These nucleation of the cracks was attributed to the weak bonding between adjacent layers consist of two different materials.

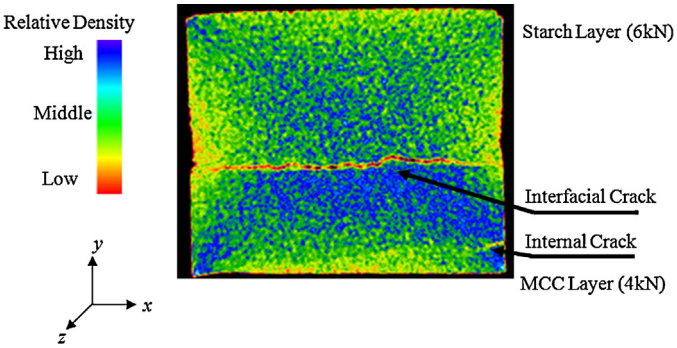

Fig. 4. X-ray micro-computed tomography cross-section images obtained after 2D reconstruction of the defective MCC–starch bilayer tablet compacted to an initial compression force of 4 kN and a final compression force of 6 kN. The image is taken at mid-height of the tablet. Interfacial crack that weakens the bilayer system can be seen between the adjacent layers (Akseli et al., 2013).

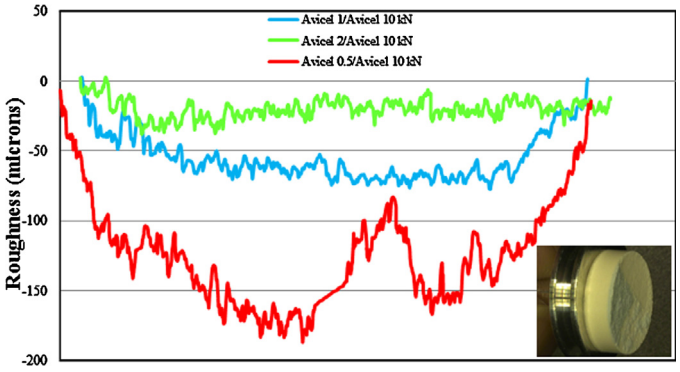

Fig. 5. Roughness profiles of the interfacial fracture surfaces of the first layer of the bilayer tablets (avicel/avicel) compressed with different first layer forces (Kottala et al., 2012b).

3.7.2. *Interface characterization tools*

The number of compressions in manufacturing of multilayer tablets is equal to the number of layers in the multilayer tablet if the first layer is not compressed before addition of second layer, there is a possibility of uncontrolled mixing of granules of first layer into second layer at the interface. In addition, if the first layer is not compressed before addition of second layer, due to the centrifugal force during the rotation of the turret, the granules of first layer may shift toward the outer periphery of the die cavity resulting in an angled (skewed) interface. A clear demarcation between the two layers is desirable since it is not only appealing but also visually assures that there is no cross-contamination. The material response of the constrained particles to an applied load within the initial compaction layer has shown to have a detrimental effect on the resistance to fracture of a bilayer tablet (Kottala et al., 2012a; Akseli et al., 2013). This indicates the importance and quality of the bonding produced at the interface (Fig. 5).

Knowledge of the morphology and surface properties of pharmaceutical particles commonly utilized in tableting applications, in a free or a consolidated state, can assist with the characterization of a material mechanical response to an applied load. The determination of the inherent structure of single particles obviously requires a topographical methodology which can accurately operate at relatively small length scales, such as atomic force microscopy. At larger operating length scales, as commonly employed with an optical profilometer, the 'waviness' or form and roughness of a surface can be determined. It is the form of a surface which may provide information regarding the elastic recovery of a compacted material (Poon and Bhushan, 1995). Previous applications of optical profilometers to investigate the properties of compacted materials have involved the generation of both 2D and 3D profiles of surfaces to be analyzed. Generally, for tablet analysis where the samples are relatively large and are considered isotropic, a repeatable line profile provides an adequate analysis (Kottala et al., 2012a). The stress distribution caused during the loading of the particles and the resultant tablet inhomogeneity are, therefore, postulated to be the cause of the tablet fracture. The fracture of tablets is the result of a crack propagating a finite distance within the sample and is commonly grouped under two dominant components: lamination (also referred as delamination) and capping. Lamination occurs when the strength of the compact is reduced by internal cracks within the tablet. Capping is where the upper part of the compact dislocates from the bulk assembly. If the delamination is due to rapid relaxation of the peripheral regions of the bilayer compact due to air entrapment during ejection from the dies, it is strongly recommended to have dies tapered either at one end or at both sides to enable air to escape from the compact.

A study conducted by Bashaiwoldu et al. (2004), using pellets exhibited that structural changes, including variations in porosity due to elastic relaxation, of the pellets could be determined from topographic measurements using stylus profilometry. The surface topography of compacts can also be used as a means to optimize compaction conditions (Okzan and Briscose, 1996). The greater the variation of the density distributions within a tablet, the greater the amount of stored stress/strain in the structure, which is released upon ejection in the form of stress relaxation. This phenomenon is dependent on the tablet geometry (flat-face vs. curved-face tablets) (Eiliazadeh et al., 2003; Jason et al., 2013).

More recently, fracture mechanic principles were introduced by Kottala et al. (2013) to evaluate the mechanical fracture strength of bilayer compacts. With experimental data, the stress intensity factor was estimated. Stress intensity factor is a measure of materials resistance to crack propagation, which is a function of Young Modulus and Poisson ratio. The authors attempted to understand the impact of physico-chemical properties of the powders, deformation histories of the layers and compression process parameters on the interfacial stress intensity factor of the bilayer compacts. Compacts made with brittle materials in the first layer offered better resistance to crack propagation compared to compacts having plastic materials in the first layer. An evaluation of the impact of water vapor on crack propagation in soda lime glass showed that critical stress intensity factor decreased with the increase in the amounts of water vapor (Wiederhorn, 1987).

3.8. *Bilayer tablet compression machines*

Several bilayer presses such as Kilian, Oystar Manesty, Hata, Korsch, Courtoy, Fette, Kilian and Piccola are commercially available for formulators and process development scientists. Most instrumented bilayer presses are equipped with control systems to automatically evaluate compression forces and punch displacements on the presses. Recent advances in the compression machine design and its accessories have provided opportunities to choose the features (first layer sampling, sealed feeders, precompression rolls, sensitivity of layers strain gauge, maximum upper punch penetration) as per the requirements of the product under question.

The level of precompression force, punch velocity, consolidation time, dwell time, relaxation time, and the applied compression force have significant effect on the critical quality attributes of the tablet (Muzzio et al., 2008). As detailed in the previous sections, separation of the two individual layers is the consequence of insufficient bonding between the two layers during final compression of the bilayer tablet. Correct bonding is only obtained when the first layer is compressed at a low compression force so that this layer can still interact with the second layer during final compression of the tablet. Bonding is severely restricted if the first layer is compressed with high compression force. The low compression force required when compressing the first layer unfortunately reduces the accuracy of the weight control mechanism since it relies on "compression force measurement" using a weight-force curve as a surrogate, indirect measurement of weight. More sensitive compression transducers may have to be installed for first layer compression to accurately detect small compression forces allowing optimum layer adhesion, as well as weight control. Applying a low compression force on the first layer is problematic from weight control stand point as the force versus weight sensitivity decreases as the force decreases (Vogeleer and De Smet, 2002). In other words, changes in weight will have less impact on the force when it is low and leads to less sensitive control over weight.

Most double-sided tablet presses with automated production control use compression force to monitor and control tablet weight. The effective peak compression force exerted on each individual tablet or layer is measured by the control system at

main-compression of that layer. This measured peak compression force [F] (under constant thickness) is the signal used by the control system to reject out-of-tolerance tablets and correct the die fill depth when required. The compression force control system is always based on measurement of compression force at main-compression and not at pre-compression since a higher compression force is required to obtain sufficient sensitivity, thus allowing a more accurate control. A weight control system based on compression force monitoring is not the best solution for first layer weight control in a bilayer tableting process. A compression force-controlled system requires a minimal compression force of several hundreds of Newtons (N). However, many bilayer formulations require a first layer compression force of less than 1000 N in order to retain the ability to bond with the second layer. Beyond 1000 N, this ability may be lost, bonding between both layers may not be sufficient, resulting in low hardness of the bi-layer tablet and separation of the two layers (unpublished data). To overcome such basic problem, which is inherent to the principle of compression force monitoring, Courtoy solved the challenge by using a different weight monitoring system based upon 'displacement' control system (Vogeleer and De Smet, 2002). "Displacement measurement" as the alternative to "compression force measurement" has the advantage that accuracy increases with reduced compression force. At higher production speed, the risk of separation and capping increase but can be reduced by sufficient dwell time at all four compression stages (pre-compression force and main compression force for each of the layer). Weight monitoring based upon 'displacement' also provides increased dwell-time in addition to good bonding between the two layers, with improved and accurate weight monitoring/control of the first layer. As claimed by Courtoy, a double-sided tablet press with "displacement measurement" can be the preferred press to produce bi-layer tablets. To compensate for a decreased dwell time (at higher press speeds) during compression, larger compression rolls and punches with special head design, extended dwell bars (introduced by Korsch) are available.

Incorporation of sensors in the compression work flow have provided insight into the potential challenges and facilitated a better control and monitoring of the compression process: ejection sensor (will help to evaluate the sticking potential in the die), take off sensor (will help to evaluate the sticking potential on the punch face), torque sensor (to measure the work required to move the powder in the feed turret), and pre and main compression force sensors (will help to reject the tablets outside the specification). Some recent model versions of presses include automated sampling and integrated multi-tester. The feedback loop will adjust the press parameters based on the weight, hardness, and thickness data determined by the tester. In the new Courtoy–Modul series press, tablet weight control is based on displacement of the punch into the die rather than the main compression force, which the manufacturer claims to have a better weight control when one of the layers has a relatively lower weight in a bilayer tablet. New model presses are equipped with software packages for data acquisition, calculate results compare parameters within and among the batches, correlate material properties to product quality, and to monitor and control the critical bilayer compression parameters. The precision needed for controlling the individual layer weight demands consistent behavior of the final blend such as flow property and particle size distribution.

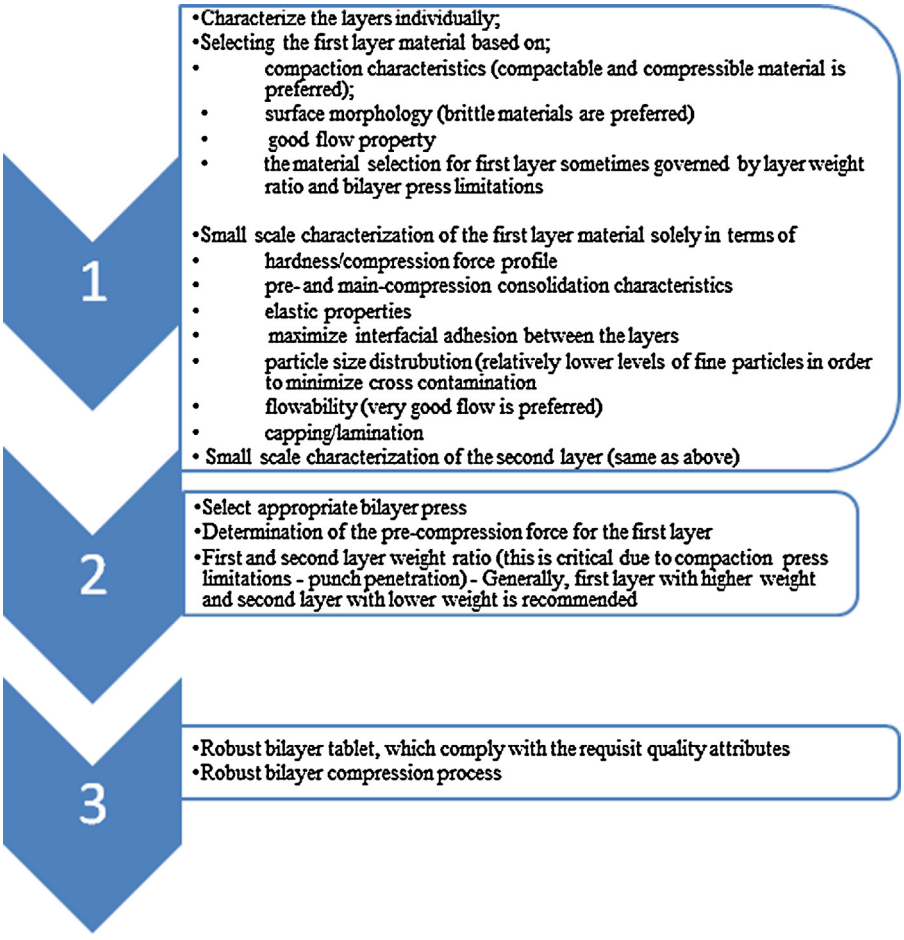

Fig. 6. Bilayer tablet characterization and manufacturing process.

When chemically incompatible APIs are used in the bilayer formulation, obtaining a well defined layer demarcation and avoiding cross contamination between the powders composing the two APIs, by removing any powder residue from the die plate is very critical. To this end, dedicated scrapers are located before and after each sealed feed shoe, to move residual powder dust to the outside of the die table, where a high efficiency suction nozzle is located in front of each feed shoe to keep the die table clean. The level of fine particles in the formulations should also be kept to a minimum as fines pass under feed shoe and scraper blades, which can lead to an increased cross contamination between the layers jeopardizing the chemical integrity of the bilayer compacts.

Many advances have also been made to reduce the cost and time and to increase the flexibility and productivity. Advent of interchangeable turrets (pioneered by Fette) has greatly reduced the time required to clean the press between the runs facilitating a faster product change over. Other modifications like openness of the structure and accessibility of KORSCH XL press versions and centrifugal die filling of IMA press will provide the flexibility in cleaning the press. Most of the recent compression machines, by almost all the vendors, have clean-in-place (CIP) option that minimizes operators contact with the product.

4. Bilayer tablet development: where to start?

The review detailed in this article related to material properties, characterization tools and bilayer compression process in view of guiding the formulation and process scientists to develop a robust bilayer product is summarized in the following schematic presentation (Fig. 6).

5. Conclusions

Bilayer and monolayer tablet manufacturing shares many common technological features as both products are formed by powder compaction. While significant advances in compaction area have brought improvements to quality and efficiency of pharmaceutical tableting in general, there are still a number of scientific and technological challenges ahead to bring bilayer design and manufacturing to similar levels of robustness as encountered in monolayer tablets. These issues range from product characterization, to material/parameters/equipment selection, as well as modeling. Bilayer tablets by design are heterogeneous systems composed of two (or more for multilayers) different layers separated by a discrete interface. This heterogeneity is the main source for the additional challenges in the design and manufacture of bilayer tablets. The properties of compacted products such as hardness and lamination tendency depend not only on the formulation but also on the deformation history of each layer during tablet manufacturing. While for monolayer tablets the impact of deformation history is reasonably well characterized and understood, for bilayer tablets it requires further studies due to the interdependency between first and second layer interactions, including thickness, weight and force. Variations in one single parameter result in changes in the properties of both layers and also the interface.

In this article, some key issues were identified for bilayer tablet manufacturing attendant to the need for understanding heterogeneous systems while providing an overview of prior and current strategies to address them. More specifically, the following critical aspects were reviewed. The role of material properties on the competition between layer and interface strength, the impact of first layer and second layer compression forces on the patterns and mechanisms of bilayer failure including the appearance of an optimal region for the selection of the first layer force and the effect of lubricant on the heterogeneity of both layers were described. In addition, the impact of layer ratio, layer sequence and layer weight control on the overall characteristics of the bilayer products were also reviewed. Bilayer tablet characterization is a key aspect toward better understanding and design, which requires additional techniques such as 3D characterization tools and interface characterization tools. A discussion of the equipment/devices available for both R&D and manufacturing environments is also included.

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