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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