Introduction

Multi-layer tablet manufacture is more complex than compacting single-layer tablets from a blend containing multiple active pharmaceutical ingredients (APIs). Multi-layer tablets offer benefits for overcoming API-API interactions and stability issues, tailoring dissolution profiles, and bringing brand recognition to finished dosage forms. Multi-layered tablets bring together differently formulated powder mixtures, which typically contain a different API, into a single tablet with two or more layers. In many cases, the layers differ in color as well for providing additional brand recognition.

Typical reasons for multi-layer tablets include:
- Incompatible API separation
- Different disintegration times for each layer
- Combination of different dissolution profiles
- Creating an easy-to-recognize brand

For multi-layer tablets manufacture, specialized tableting equipment is necessary. In addition, excipient selection is critical since the layers require certain properties, which only can be achieved using few excipients.

Excipients for multi-layer tablets

The formulation

The quality/integrity of multi-layer tablets depends on the formulation. Each layer within the tablet should be formulated individually keeping in mind the importance of the layer interfaces. Ingredient particle sizes and size distributions should be optimized to provide content uniformity within each layer, yet provide sufficient binding performance at layer interfaces forming robust tablets during compaction.

The first layer, typically the bottom layer, is the key of the formulation. The surface of the first layer should be moderately porous to provide adhesion at the interface with the second layer and so on with each additional layer. In turn, each layer must contribute sufficient compactibility for a robust and physically stable monolithic dosage form. For both, porous surface and compactibility, PROSOLV® SMCC provides excellent flexibility in multi-layer tablet formulation development and manufacture.

Microcrystalline cellulose (MCC) possesses an approximate 1 m²/g specific surface area. PROSOLV® SMCC possesses a 5 m²/g to 6 m²/g surface area, which means a five-fold surface area increase.

A significant challenge when formulating multi-layer tablets is the tablet layer interfaces, which require good adhesion. Poor adhesion may compromise dosage form integrity, causing multi-layer tablets to lose desired functionality. Issues, such as friability, lamination, and/or dissolution problems may result requiring reformulation. An appropriate formulation of the individual layers and overall tablet is the key to a good multilayer tablet.
Technical Information

compared MCC. The greater surface area provides a larger contact area between the layers of a multilayer tablet and leads to greater physical tablet stability. The surface structure of the compressed tablet depends not only on the appearance of the binder, but also on the compaction force. Below are scanning electron micrographs (SEMs) of tablets produced using PROSOLV® SMCC 90 compressed at different forces.

Even with compaction forces below 10 kN, PROSOLV® SMCC tablets offer excellent hardness and surface structure for adhesion between layers.

Recommendations advice for multilayer tablets formulations

Binder particle size should be fairly coarse to provide porous surfaces, but not so large that compaction is compromised. PROSOLV® SMCC 90 and PROSOLV® SMCC HD 90's particle is approximately 110 µm and is ideal for multi-layer tablets. Ideally, each layer should be at its individual equilibrium moisture content at the time of manufacture. If not at equilibrium moisture content, water (other residual solvents) may migrate across layer interfaces until a moisture balance results. Water transport across layer interfaces may not always adversely affect tablet integrity. In some cases, water transport across layer interfaces may initiate swelling causing weakening and leading to other issues. Additionally, solvent transport across layer interfaces could promote API instability.

The lubricant level should be as low as possible without compromising tablet ejection upon completion of dosage form manufacture. PRUV®, sodium stearyl fumarate, in place of magnesium stearate is preferred during multi-layer tablet manufacture. PRUV® is more hydrophilic and allows better binding at layer interfaces and results in overall harder tablets. since magnesium stearate can compromise tablet bond formation, not only within each layer, but at the layer interfaces, softer, laminating tablets may occur.

Avoid excipients, which undergo polymorphic (crystal habit) changes with time or when exposed to various environmental conditions. Lactose, for example, exhibits polymorphism given certain conditions. Changes in crystal habit can often weaken tablet interfaces causing layers to separate.
Tablet press

Typically, multi-layer tablets are compacted using specialized rotary tablet presses. Bi-layer presses require two compression phases, two feed areas, and one ejection position. During one turn of the press, two individual compression cycles are performed producing one bi-layer tablet.

In most modern bi-layer tablet presses, bi-layer tablet production requires six steps:

1. **Filling the die with powder for the first layer**
2. **Pre-compressing the first layer with low forces in preparation of adding the second layer**
3. **Adjusting the die volume for the second layer**
4. **Filling the die with powder for the second layer (onto the first layer)**
5. **Compressing the tablet in its entirety**
6. **Tablet ejection**

Since multiple feed areas are required during multi-layer tablet manufacture. Individual layer weight uniformity, as well as overall tablet weight uniformity, is critical. This is one of the many challenges, particularly during high-speed manufacture. This is only achieved through robust formulation development, proper equipment set-up, and rigorous sampling protocols for individual layers and finished tablets.
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