W5156

# The Influences of Binders and Fillers in the Middle Layer on the Bonding of Three-Layered Tablets

Kyung Hun Kim, Jin Seob Oh, Hyung Min Son, Sang Wook Lee, Min Jung Kim, Cho Rok Shim, Il Woo Jung, Jun Sang Park*

R&D Center, GL PharmTech, Seongnam, Gyeonggi, South Korea

* Correspondence to jspark@glpt.co.kr

CREATIVE INNOVATION FOR BETTER HEALTHY LIFE

## Introduction

- One of the big challenges in formulating multi-layer tablets is the delamination or layer separation either during manufacturing and storage[1].
- During compression or further downstream process, thermal stress during compaction of stiff materials and difference of elasticity between two layers could lead to delamination of tablets[2].
- During storage, stresses created when the layers swell differently by temperature and humidity also could cause layer separation at the interface[3].
- **Effects of fillers in the middle layer on delamination of the multi-layer tablets which had different outer-layers on storage** were investigated.

## Methods

### ❖ Formulations of three-layered tablets

- Tableting machine : MRC-37T (Sejong Pharmatech Co. Ltd., South Korea)
- Tablet weight : 1145 mg

| Batch | TL1 | TL2 | TL3 | TL4 | TL5 |
|---|---|---|---|---|---|
| Upper Layer | Immediate-release formulation with lactose and MCC | | | | |
| Middle Layer (80mg) | Microcrystalline cellulose(MCC) | | | | |
| | - | Microcelac 100 | Cellactose 80 | Lactose | Mannitol |
| | - | Copovidone (Kollidon VA64) | | | |
| | - | Magnesium Stearate | | | |
| Lower Layer | Sustained-release formulation with HPMC | | | | |

### ❖ Stability test under stressed condition

- Test items : appearance, weight, dimension, hardness and friability
- Condition : 40˚C/75%RH
- Period : 3 weeks
- Core tablets without package

## Results and Discussion

### ❖ Preparation of three-layered tablets

- **All formulation didn't show any crack** right after compression before exposure to high temperature and humidity.
- TL5 using **mannitol showed the highest hardness** in the same tableting condition.

Table 1. Hardness and friability of three-layered tablets

| | Hardness (Kp) | Friability (%) |
|---|---|---|
| TL1 | 19.2 | 0.3 |
| TL2 | 23.3 | 0.2 |
| TL3 | 23.6 | 0.1 |
| TL4 | 23.1 | 0.2 |
| TL5 | 24.8 | 0.1 |

### ❖ Changes of three-layered tablets

#### ➢ Appearance

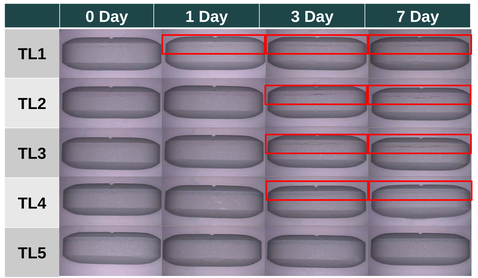


Figure 1. Delamination of the middle layer during the storage (40˚C/75%RH without package) for 7 days.

- TL1 consisting of mainly MCC showed cracks on the first day on storage.
- Only TL5 showed no crack between the layers for 7 days.
- The delamination occurred at the interface **only between the middle layer and the lower layer containing HPMC for sustained release formulation.**
- It was suggested that **different thermal strains, water affinity and swelling characteristics of two layers, mainly between MCC and HPMC, caused the delamination on storage[3,4].**

#### ➢ Frequency of delamination of three-layered tablets by high temp. and humidity

- **Delamination occurred between** the lower layer for sustained release using **HPMC** and the middle layer for immediate release using **MCC** when thermal and hygroscopic stress were given.
- Over 90% of the TL1 to TL4 tablets showed cracks between the layers.
- **TL5 showed no crack in 2 weeks and below 5% of tablets were detected delamination only after 3 weeks.**

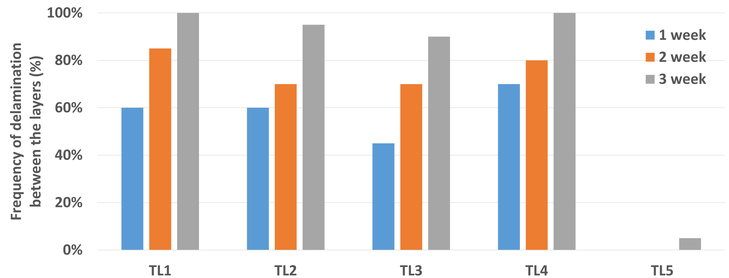


Figure 2. Frequency of delamination between the layers during the storage for 3 weeks.

#### ➢ Changes of thickness and weight of three-layered tablets

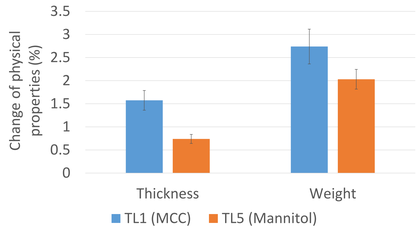


Figure 3. Changes of thickness and weight of the three-layered tablets at 40˚C/75%RH for 3 weeks.

- The change rate of thickness of TL1 was twice higher than those of TL5.
- The change rate of weight of TL1 was about 25% higher than those of TL5.
- Even though the substituted amounts of filler in the middle layer **was about 4% of the total weight of tablet**, strong effects were given on the characteristics of tablets.

## CONCLUSIONS

- **Mannitol as a filler in the middle layer supplied a better bonding strength to the layer consisting of HPMC-based formulation** than lactose and MCC during compression.
- Therefore, TL5 using mannitol showed the higher hardness and friability of tablets than those of TL1 to TL4 using lactose and MCC.
- **Because of the similar composition, the bonding strength between the upper and the middle layer** containing MCC respectively **was strong and showed no crack** when it exposed to high temperature and humidity.
- However**, the interface between the middle layer containing MCC and the lower layer containing HPMC showed delamination** of the tablet during the storage at 40˚C/75%RH without package.
- **Mannitol supplied the better bonding strength of the middle layer to the HPMC-based lower layer** for sustained release than lactose and MCC.

### ❖ References

1) C.Y. Wu, J.P.K. Seville, A comparative study of compaction properties of binary and layered tablets. *Powder Technol.*, 2009, 189, 285~294.
2) F. Podczeck, Theoretical and experimental investigations into the delamination tendencies of bilayer tablets., *Int. J. Pharm.*, 2011, 408, 102~112.
3) B.M. Zacour, P. Pandey, G. Subramanian, J.Z. Gao, and F. Nikfar, Correlating bilayer tablet delamination tendencies to micro-environmental thermodynamic conditions during pan coating. *Drug Dev. Ind. Pharm.*, 2014, 40(6), 829~837.
4) N. Kottala, A. Abebe, O. Sprockel, et al. Evaluation of the performance characteristics of bilayer tablets: part II. Impact of environmental conditions on the strength of bilayer tablets. *AAPS PharmSciTech* 2012, 13, 1190~1196.

Global Leader in Pharmaceutical Technology