

# Development of Triple-Layered Tablets Containing Laxatives with a Hydrophilic Polymer

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## Introduction

- Various kinds of laxatives such as bulking agent, stool softener, stimulant, osmotic agent have been applied for the treatment of constipation which prevail in the general population.<sup>1),2)</sup>
- Enteric coated tablet dosage form of fixed dosed combination with Bisacodyl(stimulant) and Docusate sodium(stool softener), Dulcolax-S<sup>®</sup>, was developed by Boehringer Ingelheim Pharmaceuticals, Inc.
- Bulk-forming laxatives have swelling and water adsorbing capacity to add water to stools so that they can pass more easily through lower part of intestine.<sup>3)</sup>
- In order to supply the bulk-forming and hydrating effect with inactive ingredients in a tablet, triple-layered tablet dosage form can provide a solution to develop a combinational formulation which prevents from the interaction with drug layer.

## Objective

- To develop new triple-layered tablets containing Bisacodyl and Docusate sodium with a hydrophilic polymeric layer.

## Methods

- Polymeric layer was designed by water adsorbing and mixing in High shear mixer in order to not only improve the binding capability but also exclude organic solvent and drying process.

Water(3%w/w) adsorbing to filler (High shear mixer)

Mixing sodium CMC (High shear mixer)

Screening and Posterior mixing (24mesh & V-mixer)

Triple-layered tablet compression



Manesty FlexiTab system

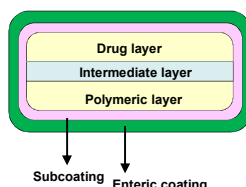
- Swelling capacity was evaluated in 50mL of pH 6.8 buffer at 37°C for 15 hrs.
- Acid resistance tests of enteric coated tablets were conducted in disintegration tester for 2 hrs.
- Drug release tests were conducted by buffer transition method for Bisacodyl/Docusate sodium tablet monograph of Korean Pharmacopoeia.
  - 1) Acid stage : 0.1N-HCl 500mL, Basket 100rpm, 2hrs
  - 2) Buffer stage : pH 7.5 buffer+1% SLS 900mL Paddle 100rpm, 1hr
- Stability test of PVDC/PVC PTP packaged product was performed under 40°C/RH75% for 3 months.

### \* References

1. Higgins PD, Johanson JF, Epidemiology of constipation in North America; a systemic review. Am J Gastroenterol 2004; 99(4): 750-759.
2. Emmanuel AV, Tack J, Quigley EM, Talley NJ, Pharmacological management of constipation. Neurogastroenterology Motil 2009; 21: 41-51.
3. Takaharu S, Fujie M, Yuju I, Kouji M, Hedeo K, Laxative and anti-diarrheal activity of polycarbophil in mice and rats. Jpn J Pharmacol 2002; 89: 133-141

## Results

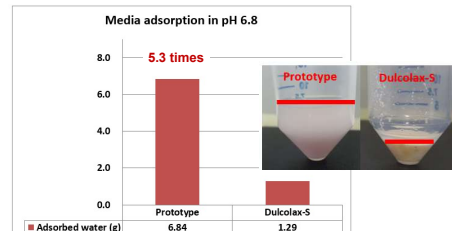
### Concept and composition of triple-layered tablets



Drug layer	Intermediate layer	Polymeric layer	Subcoating	Enteric coating
Bisacodyl Docusate sodium Corn starch MCC PH102 HPC-L Colloidal silica Mg stearate	MCC PH102 Mannitol Colloidal silica Mg stearate	Sodium CMC Silicified MCC HPC-L Colloidal silica Mg stearate Water	Hypromellose PEG 6000 Talc	Acryl-Eze II <sup>TM</sup>
Wet granulation	Mixing	Water adsorbing & mixing	80% EtOH coating	Aqueous coating
200mg	150mg	440mg	20mg	80mg

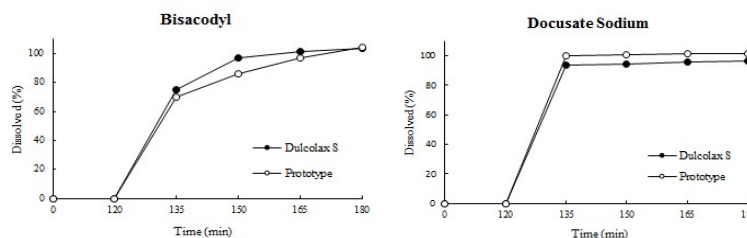
### Physical properties & Media adsorption of triple-layered tablets

Items	Results
Appearance	Oblong shaped tablet
Weight	785~801 mg
Hardness	19~23 kP / No lamination
Friability	0.26 % / No lamination
Disintegration	Drug layer <15 min Polymeric layer <3hrs



### Acid resistance and Dissolution profiles

Medium	Dulcolax-S <sup>®</sup>	Acryl-Eze I coated prototype	Acryl-Eze II coated prototype
pH 1.2	Resistant for 2hrs	Resistant for 2hrs	Resistant for 2hrs
pH 4.5	Resistant for 2hrs	Disintegrated drug layer within 30 min	Resistant for 2hrs
pH 6.8	Disintegrated within 30min	Disintegrated drug layer within 30 min	Disintegrated drug layer within 30 min



### Stability

Items	Specification	Initial	Accelerated 3 months
Appearance	Green color, oblong shape, enteric coated tablets	Complied	No change
Dissolution	0.1N HCl < 10% at 2hr	Bisacodyl 0% Docusate sod. 0%	Bisacodyl 0% Docusate sod. 0%
	pH 7.5 > 75% at 1hr	Bisacodyl 107% Docusate sod. 96%	Bisacodyl 101% Docusate sod. 97%
Assay	90.0 ~ 110.0%	Bisacodyl 99.9% Docusate sod. 98.5%	Bisacodyl 102.6% Docusate sod. 99.0%

## Conclusions

- Composition and manufacturing processes were well established to satisfy the target of physical properties of tablets, acid resistance, comparable drug release and stability.
- Small amount of water(3 w/w%) in polymeric layer played an important role for robust triple-layered tablets through providing great binding capability.
- Intermediate layer prevented effectively from the interaction between drug and polymeric layer.
- Polymeric layer with only inactive ingredients can add water to stools to expect a synergic effect with stimulant and stool softener.