The Effects of Plasticizers in the Enteric Layer on the Stability of Pantoprazole Tablets

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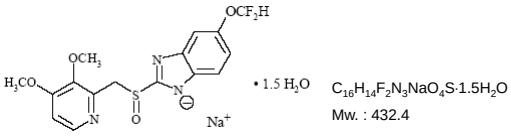
Objective

To develop a stable coating composition of pantoprazole tablets, the effects of plasticizer in the enteric layer on the physico-chemical stability were studied.

Introduction

- Pantoprazole, a substituted benzimidazole derivative, is labile to acidic environment, heat and moisture in the pharmaceutical dosage form and produce various impurities easily[1].



$C_{16}H_{14}F_2N_3NaO_4S \cdot 1.5H_2O$
Mw. : 432.4

- Pantoprazole also is formulated as enteric-coated tablets to avoid degradation by gastric acid[2].
- Many kinds of excipients interact with the active ingredient so that they could affect the critical quality attributes of drug. This improves or deteriorates the chemical stability and/or bioavailability of products.
- **Even though the stable composition of core tablet had been acquired through compatibility and stress test, general enteric coating formula could not make the products as stable as the reference, Pantoloc® tablet.**
- The effects of excipients in the enteric layer were studied and it is found out that the plasticizer was one of the most important factors to stabilize the final formulations.
- **The influences of plasticizer, triethyl citrate(TEC) and polyethylene glycol(PEG), on the stability were studied by testing impurity profile after storage under stressed conditon.**
- **The proper amount of enteric coating layer was decided by testing acid-resistance.**

Methods

- Coating machine : SFC-30 (Sejong Pharmatech Co. Ltd., Korea)
- Stability test under stressed condition
  - Test items: drug (pantoprazole) content & impurity profile
  - Condition : 60℃ in glass vials for a month
  - Analysis : HPLC : Agilent system (1100 series)
- Acid-resistance test
  - Stressed storage condition : 40℃/75%RH with no package for a week
  - Moisture uptake of products was measured by weight check.
  - Appearances of samples (6 tab) should not be changed for 2 hours in 0.1N HCl using disintegration tester.

Results

Factors and their compositions of enteric layer

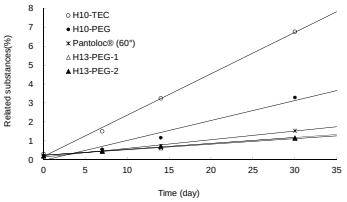
- **Factors**
  - **Amount of binder in core tablet**
  - **Kinds and amount of plasticizer**
  - **Coating amounts of enteric layer to core tablet**
- **Compositions**

Table I. Compositions for enteric coated tablets.

Code	Tablet binder amount (%w/w)	Plasticizer	Plasticizer amount (%)	Enteric layer amount (% w/w)
H10-TEC	10	TEC	12	30
H10-PEG	10	PEG	10	25
H13-PEG-1	13	PEG	10	25
H13-PEG-2	13	PEG	15	30

Effects of plasticizer on impurities and drug contents of tablets

- **Impurity**
  - **TEC(H10-TEC) was not acceptable as a plasticizer because the increase rate of impurities was 2 to over 7 times faster than that of PEG (H13-PEG-2).**
  - **3% increase (10→13) of tablet binder (H13-PEGs) showed a great positive effect.**
  - **There is no effect of PEG amount (H13-PEG-1 vs. H13-PEG-2).**



Code	Impurity increase rate (%/day)	Linearity (R2)
H10-TEC	0.2187	0.9976
H10-PEG	0.1053	0.966
H13-PEG-1	0.0294	0.9984
H13-PEG-2	0.0316	0.9957
Pantoloc®	0.0457	0.9946

Figure 1. Total impurities of coated tablets for a month under 60℃.

- **Assay**
  - **TEC(H10-TEC) also showed the most negative effect.**
  - **PEG amount had a little effects on drug content but it seemed to be insignificant.**

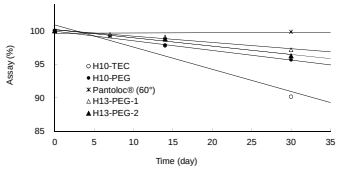


Figure 2. Assay of coated tablets for a month under 60℃.

Proper amounts of enteric layer through acid-resistance

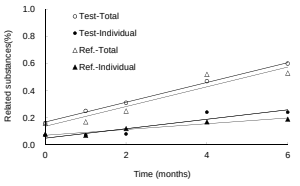
Table II. Moisture uptake and acid-resistance of coated tablets for a week under 40℃/75%RH.

Coating amounts	H13-PEG-1						H13-PEG-2		Pantoloc®	
	15%		20%		25%		15%			
	Wt. gain (%)	Acid-Resist.	Wt. gain (%)	Acid-Resist.	Wt. gain (%)	Acid-Resist.	Wt. gain (%)	Acid-Resist.	Wt. gain (%)	Acid-Resist.
0 day	0	Pass	0	Pass	0	Pass	0	Pass	0	Pass
7 day	10.37	Fail	7.96	Fail	7.12	**Pass**	9.17	Fail	8.62	Fail

- **Moisture uptake of coated tablets for a week under 40℃/75%RH was reduced as coating amount increased 15 to 25% of H13-PEG-1.**
- **Only 25%w/w of coating amount could pass the acid-resistance test after a week under 40℃/75%RH.**

Accelerated stability test of optimized composition (H13-PEG-1)

- **Accelerated stability test of enteric coated tablets for 6 months under 40℃/75%RH was conducted with the reference, Pantoloc® tablet as final package forms.**
- **Drug contents of both products, test and reference, were stable during the accelerated test (data not shown).**
- **Increase rates of impurities of H13-PEG-1 were similar with them of reference.**



<Specification of product>
- Total impurities : NMT 1.0%
- Individual impurity : NMT 0.5%

Figure 3. Total and individual impurity of final composition for 6 months under 40℃/75%RH.

Conclusions

- **Increasing tablet binder caused the positive effect on the impurity stability of pantoprazole tablet formulations.**
- **To pass the acid-resistance test, the enteric coating amount should be more than 25% of core tablet weight.**
- **Among plasticizers tested, PEG was proven to be the best one for impoving stability. On the other hand, TEC showed the negative effect on both of impurity and drug content profile.**
- **Optimized formulaition containing PEG in the enteric layer was shown to be stable and comparable to the reference.**

*** Reference**
1. S. M. Cheer, A. Prakashi, D. Faulds and H. M. Lamb, Pantoprazole, An update of its pharmacological properties and therapeutic use in the management of acid-related disorders, Drugs, 63(1), 101, 2003.
2. Protonix® Tablets, Prescription information, Wyeth Laboratories .

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