

Purpose

There are two types of hypromellose capsules, i.e., manufactured by 'cold gelling' or 'thermal gelling' dipping process, using mold pins kept at room temperature or pre-heated at 50~100°C, respectively. In addition, the 'cold gelling' requires a gelling agent such as carrageenan. We had previously carried out comparative studies on these two types of hypromellose capsules. The 'cold gelling' capsules with carrageenan and KCl showed excellent mechanical strength, i.e., less brittle, and fast disintegration with less variation.¹⁾ The fast disintegration was thought to be derived from the unique microstructure in the 'cold gelling' capsule, i.e., sea-island structure.²⁾

On the other hand, the paper by Ku *et al.*³⁾ claimed that 'cold gelling' hypromellose capsules with carrageenan could retard dissolution in acidic medium when two basic compounds with two different pKa were encapsulated, although details on APIs or excipients were not disclosed. They speculated that retardation was due to an interaction between carrageenan and these basic compounds. However, we showed the 'cold gelling' capsule, compared to the thermal gelling capsule, had even shorter rupture times, for the three structurally different basic APIs.⁴⁾ In this study, we further investigated dissolution properties of these two types of hypromellose capsules with other basic APIs.

Dissolution data⁴⁾

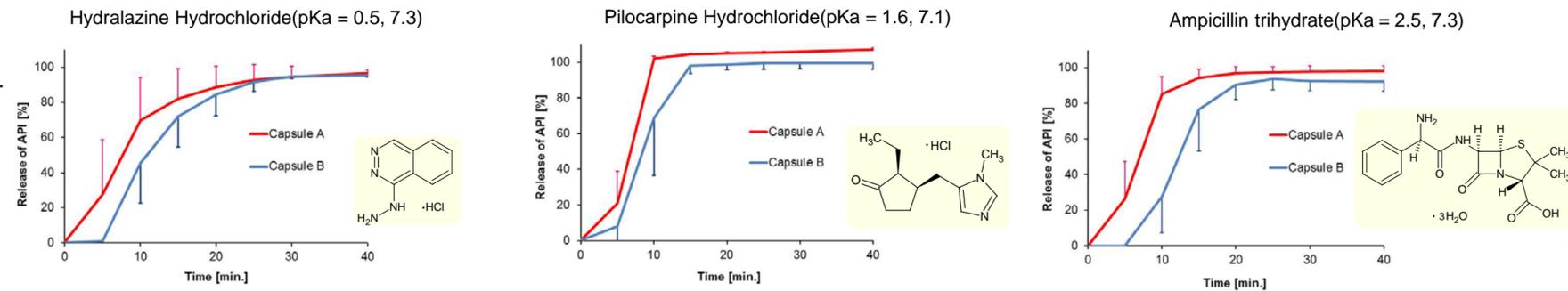


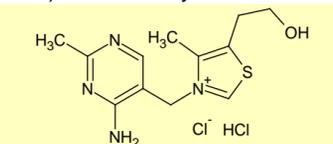
Figure 1. Dissolution profiles of basic APIs filled in HPMC capsules in 0.1N HCl at 37 °C.

Method

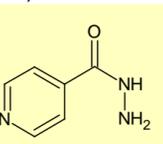
Table 1. Physicochemical and biopharmaceutical properties of basic APIs in dissolution tests.

API	Form	BCS	pKa	Fill weight [mg]	Dissolution media	Solubility [mg/mL]	Sink ratio [-]	Paddle speed [rpm]
Thiamine Hydrochloride	Salt	III ⁵⁾	4.85 ⁹⁾	50	0.1N HCl 34mM NaCl (JP 1st)	614	11,052	50
Isoniazid	Base	I/III ⁶⁾	1.82, 3.52, 10.72 ⁹⁾	100		145	1,305	
Chloroquine Diphosphate	Salt	I ⁷⁾	8.1, 10.07 ⁹⁾	100		347	3,123	
Chlorpheniramine Maleate	Salt	I ⁸⁾	4.0, 9.2 ^{10,11)}	200		243	1,092	

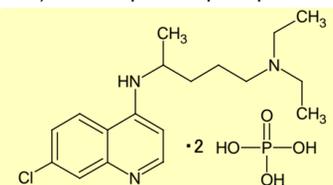
a) Thiamine Hydrochloride



b) Isoniazid



c) Chloroquine Diphosphate



d) Chlorpheniramine Maleate

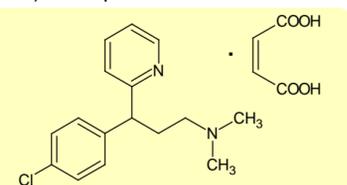


Figure 2. Chemical structure of basic APIs

Results

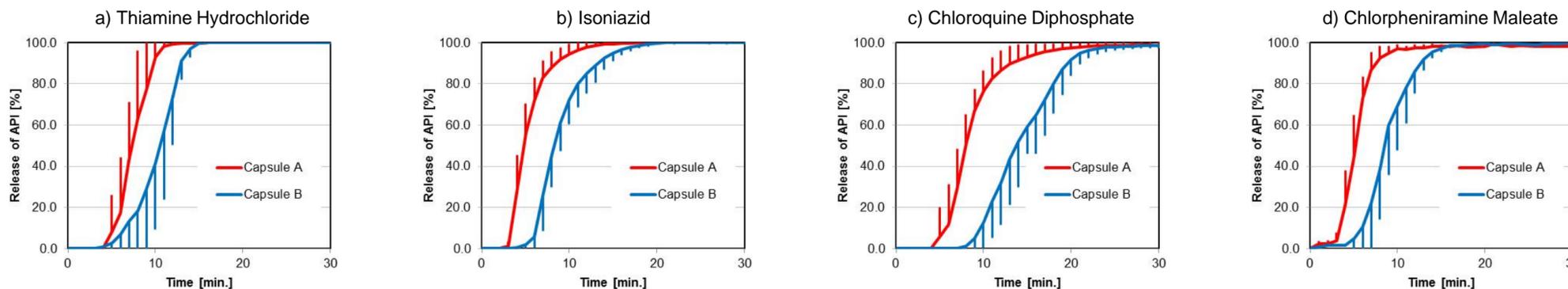


Figure 3. Dissolution profiles of basic APIs filled in HPMC capsules in 0.1N HCl, 34mM NaCl (1st fluid, JP17) at 37 °C.

- Dissolution tests showed that Capsule A compared to Capsule B had shorter rupture times and improved dissolution rates, for four structurally different APIs shown in Figure 3.
- In addition, the dissolution profiles of the Capsule A showed much less variation especially between 5 and 15 minutes.
- Results indicated no significant charge interactions between carrageenan and basic compounds in acid medium.

Conclusion

This study showed that dissolution rate from 'cold gelling' hypromellose capsules with carrageenan as a gelling agent, filled with basic APIs, showed no adverse effect in dissolution behavior in acid medium. Similar to dissolution behavior with acetaminophen in the previous studies, confirming that the excellent dissolution behavior of 'cold gelling' Capsule A with various types of basic APIs.

Reference

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