# *In vitro* drug disintegration and dissolution testing of BCS class I drug midodrine hydrochloride under simulated food-induced viscous conditions

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## Abstract

**Purpose**

The food-induced viscosity increase could significantly affect the disintegration and dissolution rates of immediate release (IR) drugs. This research is to determine the effect of food-induced viscosity on the *in vitro* tablet disintegration and dissolution of a BCS class I drug from different manufacturers. The study results may potentially help to develop better dissolution methods to simulate *in vivo* conditions.

**Results**

In this study we have used five different dissolution testing methods (as listed in Table 1) to simulate *in vivo* conditions. Five different generics brands containing 5 mg of midodrine hydrochloride but with different tablet compositions were used in the study. As the initial step all the generic tablets were subjected to standard disintegration tests using 0.1N HCl USP dissolution media and a 1% Hydroxypropyl methylcellulose (HPMC) solution (with a pH value of 1.00±0.05). All the generic tablets showed very fast disintegration times in USP media (~30 seconds) except Generic 5, which took 2.5 min. However, the disintegration times were significantly increased and Generics 4 and 5 showed very long disintegration times (~25 min) in 1% HPMC medium.

Under test method 1 in 1% HPMC medium at 50 rpm all the generic tablets showed very low drug release and with the increasing rpm the test results were over discriminative. With Method 2, Generic 5 showed a significant improvement in drug release but none of the tablets ever showed a 100% release after 2 h. Surprisingly, Method 3 showed similar dissolution profiles for Generics 3-5 regardless the decreasing of viscosity. Considering FDA recommended fed condition and taking tablet with 240 mL water, the dissolution tests were carried out with Method 4. With Method 4, Generics 3-5 showed similar dissolution profiles and showed closer to a 100% drug release within 10 minutes. It is also worth while to notice that there is a clear correlation of hardness of the generic tablets with the extent of drug release in 1% HPMC media. When hardness increases, the drug release decreased significantly for Generics 1-4. In the case of Generic 5, the nonfunctional coating governed the drug release in HPMC media. Once the coating started to dissolve, the dissolution rate of the drug improved significantly.

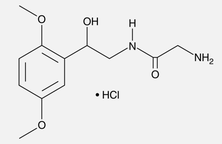
## Introduction

- Studies have shown[1-2] that an increase in viscosity of dissolution medium, simulating the ingestion of a solid meal, may impact tablet disintegration and dissolution.
- However, the impact of dynamic viscosity change inside the stomach with food intake and drug administration on drug dissolution was not fully investigated.
- Different *in vitro* dissolution methods including the ones incorporating dynamic viscosity change were explored to mimic drug intake under fed conditions in this study.
- A model drug, midodrine hydrochloride, was selected in this study as formulation composition was found to impact its bioequivalence conclusion differently under fasted and fed conditions.

1. Zaheer, K; Langguth, P. Designing robust immediate release tablet formulations avoiding food effects for BCS class 3 drugs. Eur J Pharm Biopharm. **2019**, 139, 177-185.
2. Radwan, A; Amidon, G. L.; Langguth, P. Mechanistic investigation of food effect on disintegration and dissolution of BCS class III compound solid formulations: the importance of viscosity. Biopharm Drug Dispos. **2012**, *33*, 403–416.

## Materials and Methods

Materials




- Midodrine hydrochloride is a vasopressor agent which is used as a treatment for dysautonomia and orthostatic hypotension.
- It falls under BCS class 1 due to its high solubility and high permeability.

Methods

- The fed and fasted state of the stomach was simulated by using USP 0.1 M HCl solution with and without viscosity enhancing additive, hydroxypropyl methylcellulose (1% HPMC), respectively.
- The prepared media were characterized by pH, density, surface tension, and viscosity.
- 5 mg midodrine hydrochloride tablets from 5 generic manufacturers were characterized by hardness, diameter, thickness, and weight.
- The tablet disintegration and dissolution were conducted using a disintegration tester and USP Apparatus II (paddle) in both USP medium 0.1 N HCl (USP method) and simulated food-induced viscous medium, respectively (Method 1).
- Modified test method 1 was similar to USP test, but the dissolution media was 0.1 N HCl solution containing 1% HPMC. Also the tablets were tested under three different paddle speeds (50, 75 and 100 rpm) to test the effect of paddle speed on drug release.
- Modified test method 2 was also similar to test method 1 but the dissolution time was extended to 2 hours.
- Modified test method 3 was designed to mimic gradual viscosity decrease in GI tract under fed condition. In modified method 3 the tablet dissolution started with 650 mL of 1% HPMC media, and 50 mL of USP media was added every 15 minutes until 90 minutes and total volume reaches to 900 mL.
- Modified test method 4 was designed to simulate the administration process and fed stomach. In modified method 4, the tablets were allowed swell with 50 mL of USP media for 2 min (mimicking drug taken with water), and 250 mL of 1% HPMC media was added at 2 minutes. Later another 650 mL of 1% HPMC media was added to the solution after 10 minutes.

**Table 1.** Dissolution testing methods used in the study

| | Initial Dissolution media | Initial volume of media (mL) | Stepwise addition of dissolution media | Test time (hours) |
|---|---|---|---|---|
| **USP Method** | USP media (0.1 N HCl) | 900 | N/A | 0.5 |
| **Modified Method 1 (50, 75, and 100 rpm)** | USP media with 1% HPMC | 900 | N/A | 0.5 |
| **Modified Method 2** | USP media with 1% HPMC | 900 | N/A | 2 |
| **Modified Method 3** | USP media with 1% HPMC | 650 | 50 mL of USP media every 15 minutes until 90 minutes | 2 |
| **Modified Method 4** | USP media | 50 | 1. 250 mL of 1% HPMC media after 2 minutes<br>2. Then 600 mL of 1% HPMC media after 10 minutes | 2 |

## Results and Discussion

**Table 2.** Composition of the generic tablets

| | Generic 1 | Generic 2 | Generic 3 | Generic 4 | Generic 5 |
|---|---|---|---|---|---|
| **Microcrystalline Cellulose (MCC)** | ☑ | ☑ | ☑ | ☑ | ☑ |
| **Corn starch** | - | - | - | - | ☑ |
| **Pregelatinised Starch** | ☑ | - | ☑ | ☑ | - |
| **Colloidal silicone dioxide** | ☑ | ☑ | ☑ | ☑ | ☑ |
| **Croscarmellose sodium** | ☑ | - | ☑ | ☑ | - |
| **Magnesium stearate** | ☑ | ☑ | ☑ | ☑ | ☑ |
| **Non-functional coating** | - | - | - | - | ☑ |
| **Crospovidone** | - | ☑ | - | - | - |
| **HPC (LF)** | - | ☑ | - | - | - |

**Table 3.** Characterization of each generic drug products for diameter, thickness, hardness, and weight (n=6, Ave±SD)

| Tablet Name | Diameter (mm) | Thickness (mm) | Weight (mg) | Hardness (N) |
|---|---|---|---|---|
| **Generic 1** | 8.06 | 4.02 ± 0.03 | 203.2 ± 2.2 | 49.1 ± 4.1 |
| **Generic 2** | 8.80 | 2.86 ±0.03 | 178.3 ± 0.4 | 58 ± 5 |
| **Generic 3** | 7.98 | 4.93 ± 0.01 | 252.5 ± 1.5 | 102 ± 4 |
| **Generic 4** | 7.99 | 4.20 ± 0.02 | 249.5 ± 1.1 | 130 ± 5 |
| **Generic 5** | 7.17 | 3.19 ±0.01 | 130.3 ± 0.6 | 170 ± 5 |

**Table 4.** Disintegration times of generic drug products in USP media without and with 1% HPMC with USP disintegration apparatus (n=3, Ave±SD)

| Tablet Name | Disintegration time in USP media (mm.ss) | Disintegration time in USP media containing 1% HPMC media (mm.ss) |
|---|---|---|
| **Generic 1** | 0.26 | 12.24 ± 00.15 |
| **Generic 2** | 00.17 ± 00.07 | 12.23 ± 01.18 |
| **Generic 3** | 00.16 ± 00.01 | 14.34 ± 00.36 |
| **Generic 4** | 00.36 ± 00.02 | 24.19 ± 01.32 |
| **Generic 5** | 02.33 ± 00.01 | 27.23 ± 00.14 |

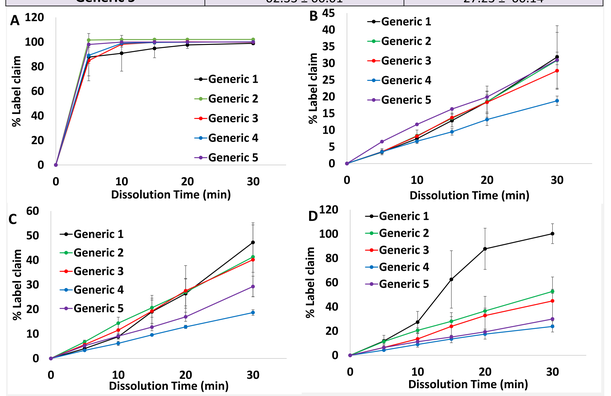



**Figure 1.** Dissolution profiles of all generic products with USP method (A), with 1% HPMC at 50 rpm (B), 1% HPMC media at 75 rpm (C), 1% HPMC media at 100 rpm (D) using modified method 1 (n=3, Ave±SD)

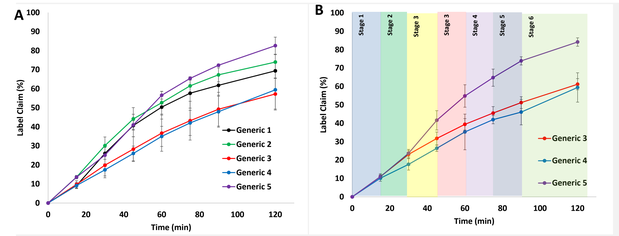



**Figure 2.** Dissolution profiles of all five generic tablets using modified Method 2 (A) and modified Method 3 (B) (n=3, Ave±SD )

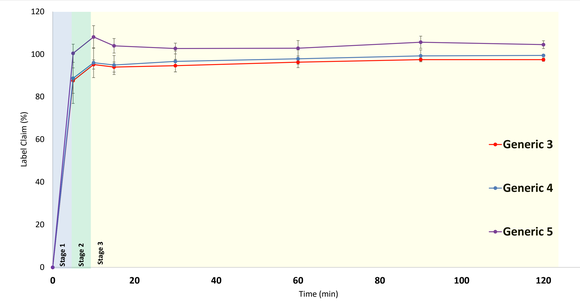



**Figure 3.** Dissolution profiles of Generics 3-5 tablets using modified Method 4 (n=3, Ave±SD)

## Conclusions

- Several non-compendial dissolution methods have been developed to simulate *in vivo* fed conditions to mimic the food induced viscosity of the stomach.
  - Methods 3 and 4 simulate the dynamic viscosity change of the stomach with the introduction of food and drug administration.
- The disintegration and dissolution was significantly slowed down with viscous media (Method 1). Furthermore, dissolution profile was more sensitive to tablet hardness change and formulation composition when dissolution study was conducted in viscous media (Method 1) than USP media (Method 0). Longer sampling time is needed for dissolution study in viscous media (Method 2).
- When dynamic viscosity change of the stomach was simulated (Methods 3 and 4), there is little change in dissolution profile between Methods 2 and 3 but significant faster release was observed in Method 4.
- More studies are ongoing to understand tablet swelling behavior in viscous dissolution media and explore the utility of these dissolution methods to predict *in vivo* performance.
  - Conduct texture analysis to investigate the effect of swelling behavior on tablet disintegration and dissolution.
  - Investigate the relationship of *in vitro* dissolution with *in vivo* pharmacokinetics (PK) data.

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