Poster# T5017

Mechanical Response of Nifedipine Extended-Release Tablet during In-Vitro Dissolution Testing*

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PURPOSE

The in vitro dissolution profiles of extended-release (ER) tablets with matrix-based formulations may exhibit a different extent of pH-dependence compared to that of a therapeutically equivalent product based on osmotic pump design. This change in dissolution behavior may cause matrix-based ER products to be vulnerable to gastric pH changes in vivo that may occur in patients with abnormal gastric pH or concomitantly taking over-the-counter (OTC) proton pump inhibitors (PPIs). In vivo studies also show that some polymer based formulations produce more rapid rises in plasma nifedipine concentrations that lead to more abrupt falls in blood pressure and trigger activation of the sympathetic nervous system. The objective of this study focuses on the mechanical properties of osmotic pump and polymer matrix-based formulations in dissolution media and the potential impacts that media pH and simulated gastric contraction have on drug release.

METHODS

Two strengths (30mg and 60mg) of osmotic pump nifedipine product A and polymer matrix-based nifedipine product B were used in this study. Dissolution testing was conducted using USP II apparatus at 50 rpm in 37°C 900 mL buffer (pH 1.2, 4.5 and 6.8) with 1% sodium laurel sulfate (SLS) as the dissolution medium for 24 hours. An in-house system was developed with the capability of monitoring product mechanical properties during dissolution testing. The simulated gastric contractions were applied to the sample during dissolution testing. The tests using in-house apparatus were conducted in 37°C 350 mL of the same dissolution medium as used for USP methods for 24 hours. Both drug release profiles and sample mechanical responses were obtained simultaneously.

***DISCLAIMER:** The findings and conclusions have not been formally disseminated by FDA and should not be constructed to represent any Agency determination or policy.

RESULTS

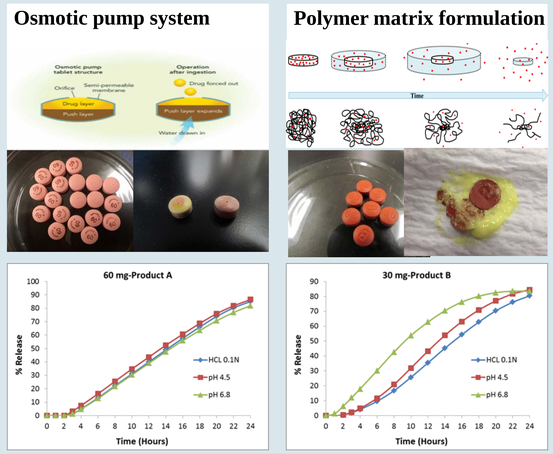

Figure 1. Comparison of dissolution profiles of Product A (osmotic pump) and B (polymer matrix formulation) in three different pH media.

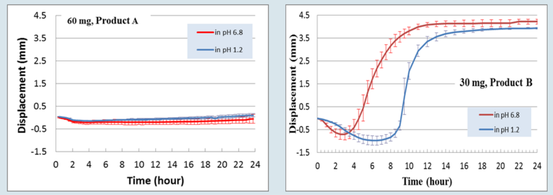

Figure 2. The displacement of Product A and B during dissolution testing in two different media.

- As shown in Figure 1, the osmotic pump formulation delivers drug substance at a constant (zero-order) rate, largely independent of physiologic factors (i.e. medium pH and gastric contraction) until the formulation is exhausted.
- In Figure 2, the matrix-based tablet swelled to about 23% of its original height in the HCl medium at pH 1.2 in 7 hours, whereas the polymer matrix lost its mechanical resistance in 10 hours during dissolution testing. In a pH 6.8 phosphate buffer, the matrix-based tablet swelled less (15% of its original height), was relatively faster to reach its highest point (in 3 hours), and lost its mechanical resistance sooner in 5 hours.

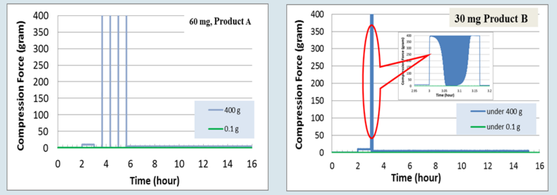

Figure 3. Illustration of simulated gastric contractions applied to Product A and B in pH6.8 phosphate buffer.

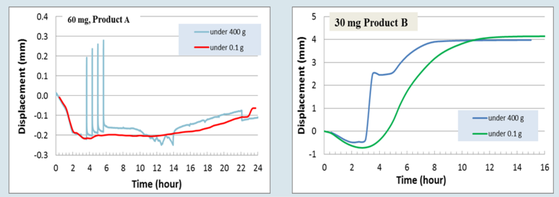

Figure 4. The displacement of Product A and B during dissolution testing with and without 400 g force in pH 6.8 buffer solution.

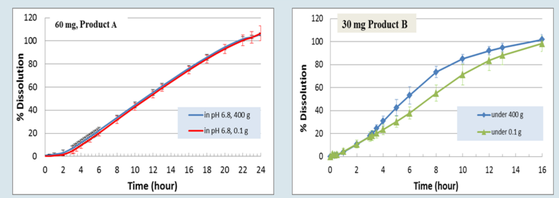

Figure 5. Comparison of dissolution profiles of Product A and B under compression in pH 6.8 buffer.

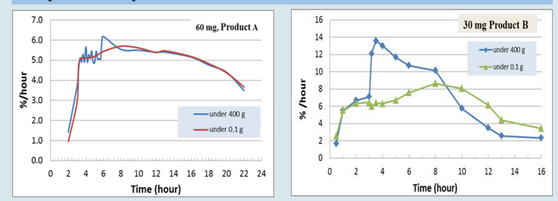

Figure 6. The dissolution rate (%/hr) of Product A and B during dissolution testing in pH6.8 phosphate buffer under different compression forces.

- Under 400 g compression (Figure 4 - 6), the polymer matrix formulation showed a greater than two-fold increase in dissolution rate (i.e. dose dumping).

CONCLUSIONS

- Compared to the osmotic pump formulation, the mechanical properties of polymer matrix-based formulation changed significantly in various pHs or under simulated gastric contraction.
- Contraction-induced dose-dumping from the matrix-based polymer formulation was observed. The results suggest that matrix-based polymer products bear a risk of formulation-related interactions during the drug dissolution process, especially in the case of concomitant pH and gastric contractile changes.
- A dissolution apparatus which can apply compression forces will aide formulation scientists performing product development and provide the regulatory agency with additional measurements to assure the quality of such drug products.

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