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Effect of Simulated Gastrointestinal Contraction on Drug Release of Nifedipine Extended-Release Tablet *

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PURPOSE

Nifedipine drug product was first introduced in the mid-1970s for the prevention of angina symptoms and later for the treatment of hypertension. The development of the extended release (ER) formulation aimed to delay and flatten the attainment of the peak plasma concentrations of nifedipine in the pharmacokinetic profiles and result in a smooth, more gradual onset of the antihypertensive effect, which can be sustained throughout 24 hours without discernible cardio acceleration. When passing through the stomach and small intestine, oral dosage forms are normally subjected to physical shear and grinding forces as well as pressure exerted by peristaltic movements. The complex physical forces exerted by the gastrointestinal (GI) tract are not well simulated by USP dissolution methods in a stirred medium. As a result, the in vitro dissolution data based on USP methods may not be correlated to in vivo drug release. Since the delivery rate of nifedipine into the systemic circulation is a direct determinant of the onset rate of the vasodilator effect, there may be potential risks to the patients if the in vitro dissolution testing is not discriminative as a quality control method.

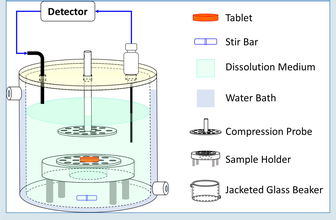
OBJECTIVE(S)

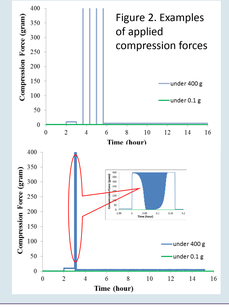
This study is to develop a bio-relevant method to explore nifedipine drug release from ER drug products under various simulated GI contractions.

METHOD(S)

60 mg of osmotic pump product A and polymer matrix based product B and C were tested in this study. An in-house system (Figure 1) was used for dissolution testing in 350 mL of pH 6.8 buffer with 1% sodium laurel sulfate (SLS) under various mechanical compression forces (0.1, 50, 100, 200 and 400 gram). Both the drug release profile and sample mechanical responses were obtained simultaneously from tests using the in-house system. Dissolution testing was also conducted as a control using USP II apparatus in 37°C 900 mL pH 6.8 buffer with 1% sodium laurel sulfate (SLS) at 50 rpm for 24 hours.

Figure 1. Schematic illustration of the in-house dissolution apparatus with applied mechanical stress





RESULT(S)

Table 1. Physical properties of drug products

	Hardness [N]	Diameter [mm]	Thickness [mm]	Weight [mg]
Product A 60mg	375.6 ± 18.1	10.6 ± 0.1	6.6 ± 0.1	555.6 ± 6.0
Product B 60mg	145.5 ± 4.0	9.3 ± 0.1	4.7 ± 0.1	321.2 ± 4.1
Product C 60mg	98.6 ± 5.3	9.2 ± 0.1	4.6 ± 0.1	308.2 ± 3.0

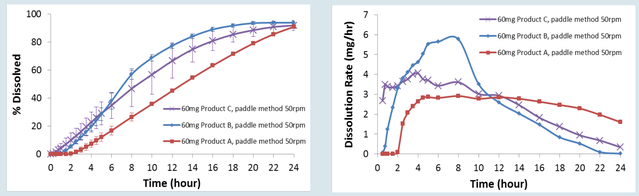


Figure 3. Dissolution profiles of three ER nifedipine formulations from USP paddle method at 50 rpm in 900 mL pH6.8 buffer.

Dissolution results from the USP paddle method showed that Product B and C exhibited faster release than Product A. Product C showed higher variability than the other two products.

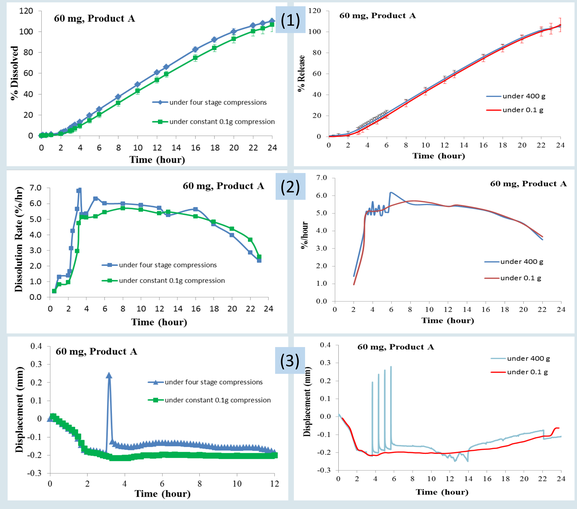


Figure 4. %Dissolution (1) and dissolution rate (2) of Product A under applied compression forces (3).

Product A showed similar dissolution behavior under various levels of applied mechanical compressions. The deformation of Product A tablet resulted in ~ 7.5% decrease in tablet height under 400 gram force compression.

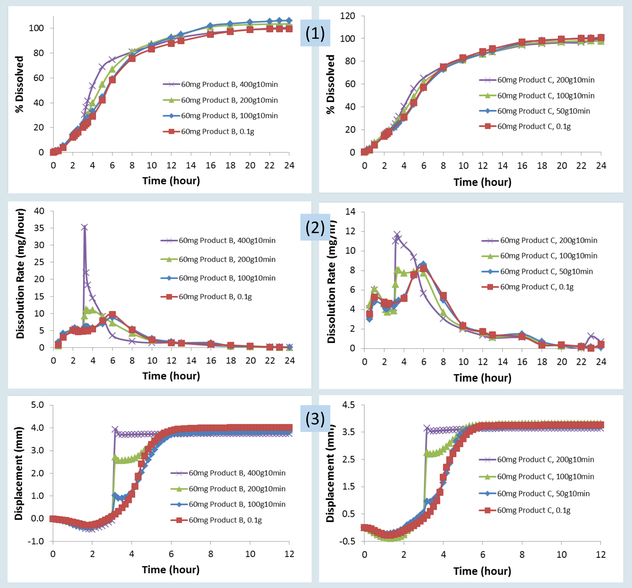


Figure 5. %Dissolution (1) and dissolution rate (2) of Product B and C under applied compression forces (3).

Product B and C showed drug release rate increases as the mechanical compression forces were increased. The Product B deformed about 22%, 58% and 84% under 100, 200 and 400 gram force compressions, respectively. The Product C had about 20%, 59% and 78% deformations under 50, 100 and 200 gram force compressions, respectively.

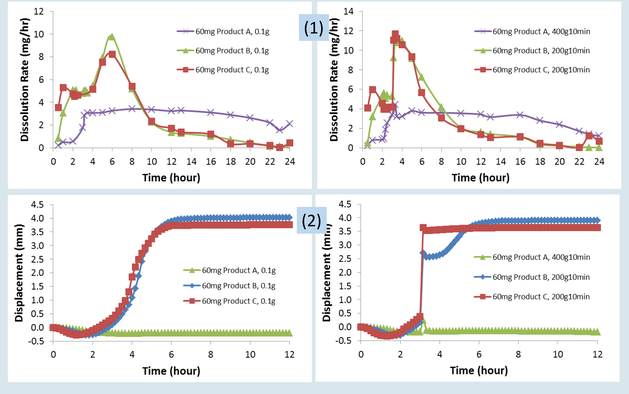


Figure 6. Dissolution rates (1) of Product A, B and C under applied compression forces (2).

CONCLUSION(S)

- The in-house apparatus is able to provide compression forces under programmable level and frequency possible to simulate GI physiological contraction for different age, gender or healthy conditions.
- The osmotic pump formulation (Product A) delivered drug substance at a constant rate, largely independent of the mechanical compression applied in this study.
- The shape and the size of the Product A tablets were almost unchanged compared to the intact tablets after testing in dissolution medium.
- The polymer based tablets (Product B and C) in dissolution medium swelled in the first 90 minutes, then became soft and gradually gave up its mechanical resistance in 6 hours.
- Compared to the osmotic pump formulation, the mechanical response of Products B and C deformed significantly under compression. The various levels of simulated GI compressions resulted in different drug release rates.
- The mechanical response during dissolution could be used as one of the parameters to assure product quality.

REFERENCE

1. G L Amidon, H Lennernas, V P Shah, and J R Crison, 1995, A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability, Pharm Res, 12:413-420.
2. A Dokoumetzidis, P Macheras, 2006, A century of dissolution research: From Noyes and Whitney to the Biopharmaceutics Classification System, International Journal of Pharmaceutics 321, 1–11.
3. B S Schug, E Brendel, D Wolf, M Wonnemann, M Wargenau, H H Blume, Formulation-dependent food effects demonstrated for nifedipine modified-release preparations marketed in the European Union, European Journal of Pharmaceutical Sciences 15 (2002) 279–285
4. P A Meredith, H L Elliott, A review of the gastrointestinal therapeutic system (GITS) formulation and its effectiveness in the delivery of antihypertensive drug treatment (focus on nifedipine GITS), Integrated Blood Pressure Control, 2013:6 79-87
5. P T Pollak, R J Herman, and R D Feldman, Therapeutic differences in 24-h ambulatory blood pressures in patients switched between bioequivalent nifedipine osmotic systems with differing delivery technologies, Clin Transl Sci, 2017, 10, 217–224
6. Z Gao, In Vitro dissolution testing of gelatin capsules with applied mechanical compression-a Technical Note, AAPS PharmSciTech, Vol 18, 231, 2017.
7. Kong F, Singh RP, 2008, Disintegration of Solid Foods in Human Stomach, Journal of Food Science, Vol. 73, Nr. 5, 67-80.

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