Dissolution Testing of Nifedipine ER Tablet Using the USP Flow-Through Method

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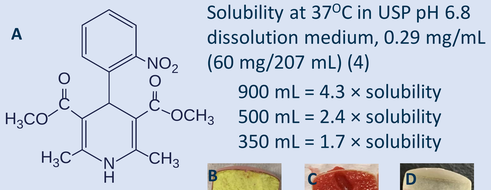
PURPOSE

Nifedipine is a Biopharmaceutical Classification System (BCS) II drug and a calcium channel blocker to manage angina and hypertension. For nifedipine extended-release (ER) tablets, four out of eight compendial dissolution tests use USP 2 paddle method with 0.5 – 1% of surfactant and 900 mL of dissolution medium (1). USP 4 flow-through method is believed to have potential advantages over USP 2 paddle method especially for drugs featuring poor water solubility, including continuous extraction of the drug, a better simulation of drug absorption and a better reflection of the in vivo drug behavior. The **objectives** of this study were 1) to investigate the effect of agitation rate and medium volume on USP 2 dissolution profile; 2) to investigate the effect of flow rate, flow type and medium volume on USP 4 dissolution profile; 3) to compare USP 2 and USP 4 dissolution profiles at various conditions.

METHODS

Nifedipine osmotic pump tablets (60 mg) (n = 3 - 12) and current USP dissolution media containing 1% sodium laurel sulfate were used. USP 2 and USP 4 conditions are specified in Results. The dissolution profiles are presented as mean ± SD. The zero order release constants were calculated using DDSolver and converted to mg/h (2).



Solubility at 37^{O}C in USP pH 6.8 dissolution medium, 0.29 mg/mL (60 mg/207 mL) (4)

900 mL = 4.3 × solubility
500 mL = 2.4 × solubility
350 mL = 1.7 × solubility

Figure 1. Nifedipine structure (A), nifedipine osmotic pump before (B) and after (C) complete release and the tablet shell (D).

RESULTS

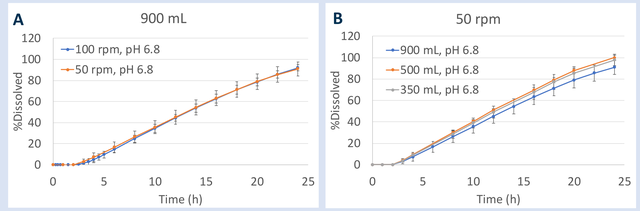


Figure 2. USP 2 dissolution profiles. The dissolution lag time and mechanism were not altered by the tested conditions.
The dissolution rate was not affected by the tested agitation rates.

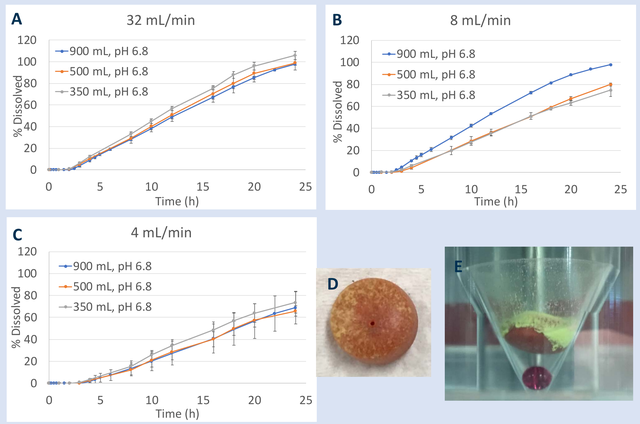


Figure 3. USP 4 dissolution profiles grouped by flow rate, turbulent flow, and representative tablet pictures at the end of the tests.
(A) at 32 mL/min, the dissolution profiles were similar regardless of the dissolution medium volume;
(B) at 8 mL/min, the dissolution rates in 500 mL and 350 mL were 2.27 mg/h and 2.20 mg/h, respectively. Both were slower than 3.09 mg/h in 900 mL. At 24 h, the %dissolved in 500 mL and 350 mL were 79.9% and 74.8% respectively, compared to 97.9% in 900 mL.;
(C) at 4 mL/min, the dissolution profiles were similar again regardless of the dissolution medium volume. The variation of %dissoved at each timepoint was larger compared to 32 and 8 mL/min. All the dissolution rates were slower than 2.1 mg/h. At 24 h, none dissolved more than 75%;
(D) shows the osmotic pump at 24 h at 32mL/min in 900 mL. Essentially all nifedipine were released and dissolved;
(E) shows the osmotic pump after 24 h at 4mL/min in 900 mL. The yellow nifedipine was released from the tablet but not dissolved into the dissolution medium.

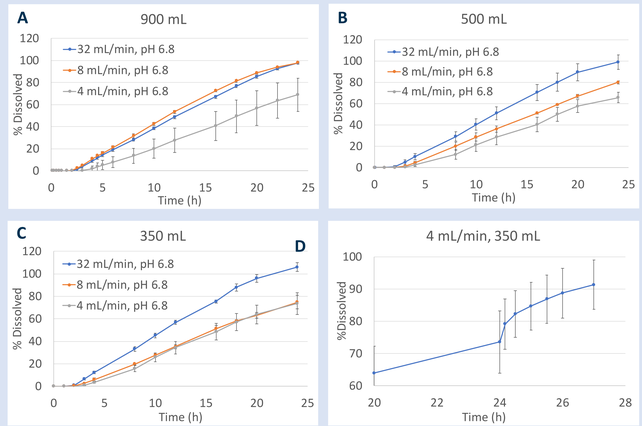


Figure 4. USP 4 dissolution profiles grouped by flow rate, turbulent flow.
(A) in 900 mL, the dissolution profile started to show a difference at 4 mL/min;
(B) in 500 mL, the dissolution profile at 8 mL/min already started to show a difference, but the dissolution at 8 mL/min was still faster than at 4 mL/min;
(C) in 350 mL, the dissolution profile also started to show a difference at 8 mL/min, but the dissolution at 8 mL/min was similar to 4 mL/min;
(D) to verify the effect of flow rate, the flow rate was increased to 32 mL/min after 4ml/min for 24 hours, 350 mL. The dissolution rate increased from 2.02 mg/h (0 – 24 h) to 9.76 mg/h (24 – 24.5 h). The rate was even higher than that of 32 mL/min, 900 mL probably because there was a pool of nifedipine already released but not dissolved, which suggested the release was the rate-limiting step at high flow rate and in high medium volume, such as 32 mL/min and 900 mL; but the dissolution was the rate-limiting step at low flow rate and low medium volume, such as 4 mL/min and 350 mL/min.

Table 1. Dissolution profile comparison of USP 2 and USP 4 in 900 mL

Condition	K_0 (mg/h)	%Dissolved at 24 h
USP 2, 50 rpm	2.51	90.9 ± 6.8
USP 4, 32 mL/min	2.64	97.6 ± 1.2
USP 4, 8 mL/min	2.72	97.9 ± 0.6
USP 4, 4 mL/min	1.78	66.1 ± 14.0

Zero Order Release of Nifedipine Osmotic Pumps $Q=K_0\times(t-T_{lag})$

CONCLUSIONS

- Variations in agitation rate and dissolution medium volume did not affect the dissolution rate using USP 2 paddle apparatus.
- At a high flow rate (32 mL/min), the dissolution profile was not affected even at non-sink condition (500 and 350 mL) using USP 4 flow through cells.
- At a low flow rate (4 mL/min), the dissolution was slower and incomplete even at sink condition (900 mL) using USP 4.
- When the flow rate was at 8 mL/min, the dissolution profile was complete at sink condition (900 mL) but slower and incomplete at non-sink condition (500 and 350 mL).
- The dissolution profiles obtained from USP 2 and USP 4 apparatus at sink condition were similar except at 4 mL/min using USP 4.
- The amount of nifedipine released from the osmotic pump at the end of 24 h was not affected by the dissolution condition.
- Future studies include the investigations of more biorelevant conditions and the to assist the establishment of a in vitro in vivo correlation (IVIVC).

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