Exploring Factors Affecting Nifedipine Biphasic Dissolution Profile Using an inForm Platform

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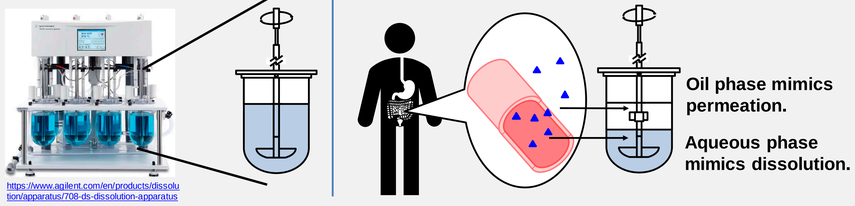
Background

There have been growing interests about the utility of biphasic dissolution testing (Figure 1) to establish in vitro and in vivo correlation (IVIVC) for biopharmaceutics classification system (BCS) class II and IV drugs. Nifedipine is a BCS II drug that may lead to severe side effects if its plasma concentrations are too high. Biphasic dissolution testing has been used for nifedipine but there is a lack of systematic investigation about the impact of testing conditions on drug dissolution.



https://www.agilent.com/en/products/dissolution/apparatus/708-ds-dissolution-apparatus

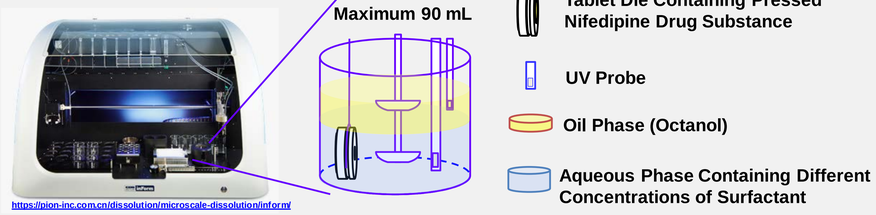
Figure 1. Illustration of a compendial paddle dissolution apparatus (shown on the left) and the proposed biphasic dissolution (shown on the right).

Purpose

To evaluate the effect of in vitro testing conditions on biphasic dissolution profile of nifedipine

Methodology

Nifedipine drug substance was used to eliminate the interference from excipients in this exploratory study. Effects on solubility and the octanol-water partition coefficient were tested by shake flask method at 37°C. Biphasic dissolution studies were performed on Pion-inForm (Figure 2), which is an automated platform that can perform biphasic dissolution experiments in low media volume.



https://pion-inc.com.cn/dissolution/microscale-dissolution/inform/

Figure 2. The Pion-inForm platform

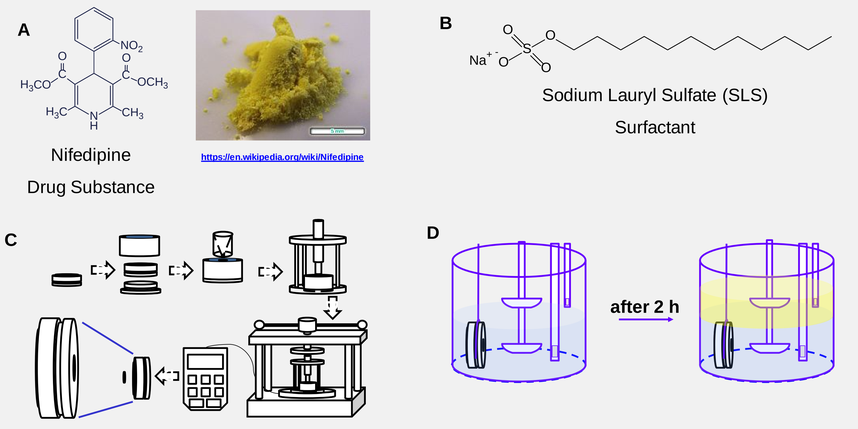
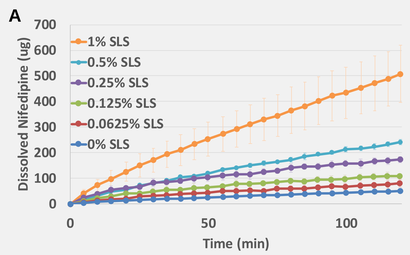
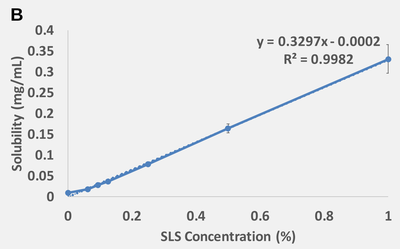


Figure 3. Nifedipine is a yellow drug substance (A). Sodium lauryl sulfate (B) is used as the surfactant in the aqueous phase of the dissolution medium. Nifedipine powder is pressed into a 6 mm tablet (C), and the dissolution is tested at various conditions (D).

Results





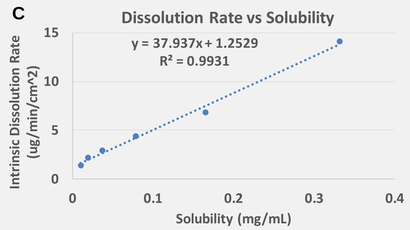
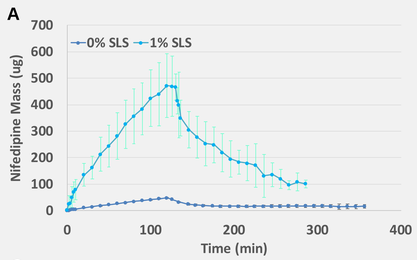
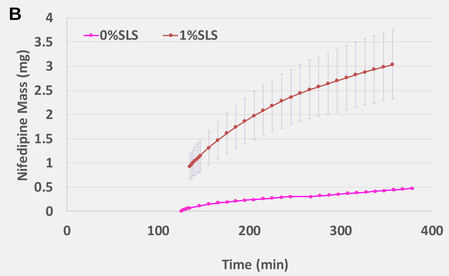


Figure 4. Nifedipine dissolution rate (A) and solubility (B) increases with increasing SLS concentration in the dissolution medium. The dissolution rate is in good linear relationship with the solubility. (40 mL aqueous phase, 100 rpm, n=3)





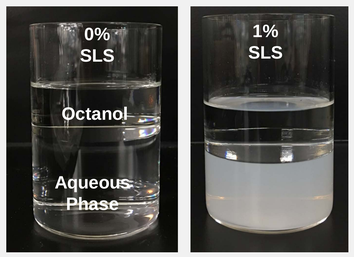


Figure 5. Nifedipine biphasic dissolution profile examples. SLS increases the dissolution rate in aqueous phase and the permeation rate into the octanol phase (40 mL aqueous phase, 100 rpm).

(A) Nifedipine concentration in the aqueous phase increases until octanol addition. Then the concentration decreases and eventually plateaus.

(B) Nifedipine concentration in the octanol phase increases with time.

(C) Octanol causes turbidity in SLS-containing aqueous phases.

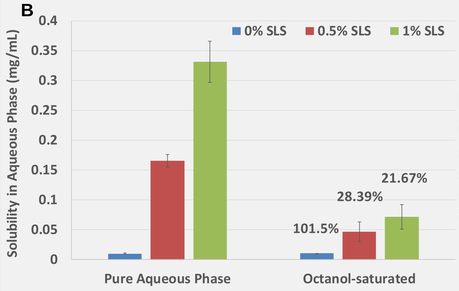
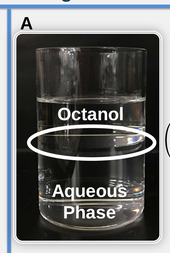


Figure 6. Effect of saturation on solubility.

(A) Solubility testing

(B) In SLS-containing aqueous phases, octanol saturation greatly decreases nifedipine solubility (the percentages are in comparison to corresponding pure aqueous phase).



Partition Coefficient = $\left(\frac{Concentration\ in\ organic\ phase}{Concentration\ in\ aqueous\ phase}\right)$

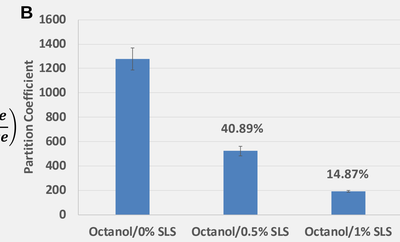


Figure 7. Partition occurs where the two immiscible phases meet (A). Surfactant decreases nifedipine partition coefficient in the octanol/aqueous system (the percentages are in comparison to Octanol/0%SLS) (B).

Table 1. Parameters of the Screening Design of Experiments (DOE)

Parameters	High	Low
Surfactant Content (%)	1	0
Aqueous Phase Volume (mL)	55	40
Agitation Rate (rpm)	100	25

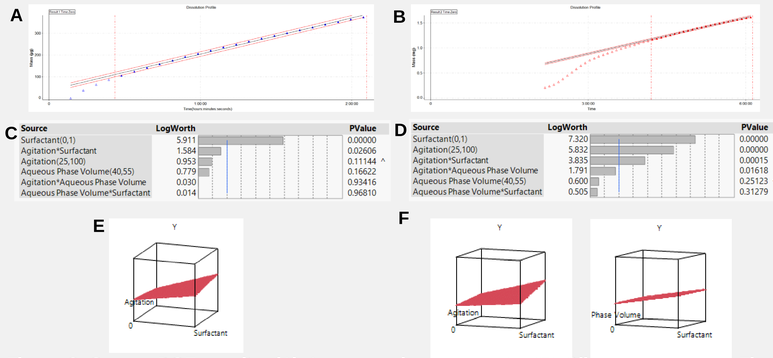


Figure 8. Screen DOE results. (A) Aqueous phase example. (B) Oil phase example. The dissolution rate calculation, parameter significance analysis and, the response surface of significant parameters of the aqueous phase (A, C and E) and the oil phase (B, D and F).

Conclusions

The effects of surfactant content, agitation rate, aqueous phase volume, along with the interactions between (1) the surfactant content and the agitation rate, (2) the surfactant content and the aqueous phase volume and (3) agitation rate and the aqueous phase volume on the biphasic dissolution profile of nifedipine were investigated.

- Surfactant content and the interaction between agitation and surfactant content were identified as the statistically significant factors on the aqueous phase dissolution profile. Increasing the surfactant content and the agitation rate increases dissolution in the aqueous phase.
- Surfactant content, agitation rate and the interactions between 1) surfactant content and agitation rate and 2) agitation rate and aqueous phase volume were identified as the statistically significant factors on the transfer profile into the oil phase. Generally speaking, increasing surfactant content and agitation rate increases the permeation into the oil phase.
- For the aqueous phase, with a fixed agitation rate and dissolution medium volume, the nifedipine drug substance dissolution rate is proportional to the solubility in the aqueous phase, which is in turn proportional to the surfactant content.
- Octanol-saturation decreases nifedipine solubility in the surfactant-containing aqueous phase.
- Increasing surfactant content decreases nifedipine partition coefficient in the octanol/aqueous system.
- The results will be translated in a full sized paddle apparatus in the biphasic dissolution of the nifedipine extended-release tablets for IVIVC establishment.

Acknowledgements

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