W0930-06-37

Exploring Factors Affecting Nifedipine Biphasic Dissolution Profile Using an inForm Platform

Li Tian[1], Moriah H. Swoboda[2], Fuxing Tang[3], Ho-Pi Lin[4], Wenlei Jiang[3], Connie Ruzicka[1], Jason Rodriguez[1] and Zongming Gao[1]

[1]Division of Pharmaceutical Analysis, Office of Testing and Research, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, St. Louis, MO 63110
[2]Biochemistry and Biotechnology, University of Missouri-St. Louis, St. Louis, MO 63121
[3]Office of Research and Standards, Office of Generic Drugs, [4]Division of Biopharmaceutics, Office of New Drug Products, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD 20993

CONTACT INFORMATION: Li.Tian@fda.hhs.gov

aaps PharmSci 360

Advancing Pharmaceutical Sciences, Careers, and Community

PURPOSE

There has been growing interest in the utility of biphasic dissolution testing (Figure 1) to establish *in vitro in vivo* correlations (IVIVCs) for biopharmaceutics classification system (BCS) class II and IV drugs. Nifedipine is a BCS II drug that may lead to severe side effects if the plasma concentration is 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 the drugs dissolution.

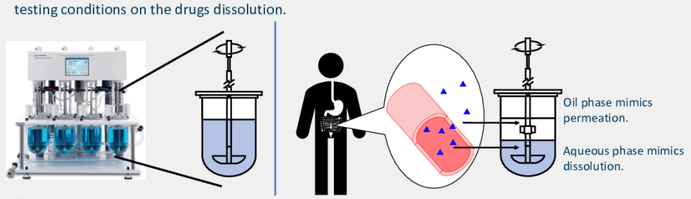


Figure 1. Illustration of a compendial paddle dissolution apparatus (shown on the left) and the proposed biphasic dissolution (shown on the right).

OBJECTIVE(S)

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

METHOD(S)

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

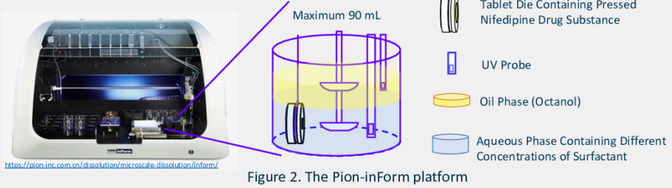


Figure 2. The Pion-inForm platform

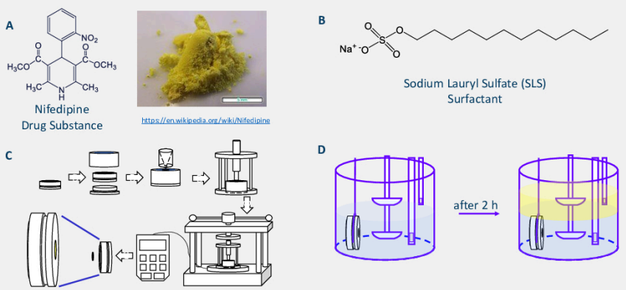
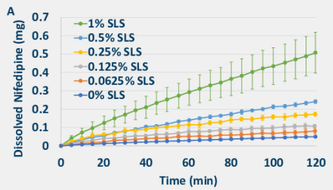


Figure 3. Nifedipine is a yellow drug substance (A). Sodium lauryl sulfate (B) is used as the surfactant in the aqueous phase of the dissolution medium. Nifedipine powder is pressed into a 6 mm tablet (C), and the dissolution is tested at various conditions (D).

RESULT(S)



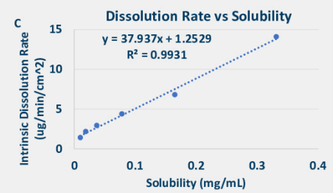
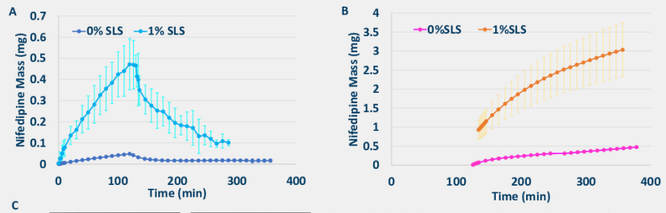


Figure 4. Nifedipine dissolution rate (A) and solubility (B) increases with increasing SLS concentration in the dissolution medium. The dissolution rate is in good linear relationship with the solubility (C). (40 mL aqueous phase, 100 rpm, n=3)



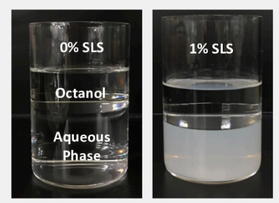


Figure 5. Nifedipine biphasic dissolution profile examples. SLS increases the dissolution rate in aqueous phase and the permeation rate into the octanol phase (40 mL aqueous phase, 100 rpm).

(A) Nifedipine concentration in the aqueous phase increases until octanol addition where 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. Solubility Testing

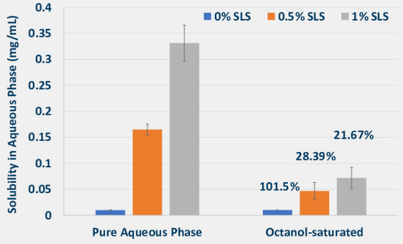


Figure 7. Effect of saturation on solubility. In SLS-containing aqueous phases, octanol saturation greatly decreases nifedipine solubility (the percentages are in comparison to corresponding pure aqueous phase).

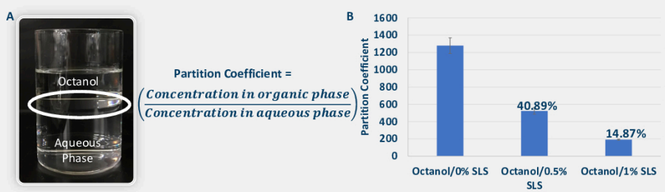


Figure 8. Partition occurs where the two immiscible phases meet (A). Surfactant decreases nifedipine partition coefficient in the octanol/aqueous system (the percentages are in comparison to Octanol/0%SLS) (B).

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

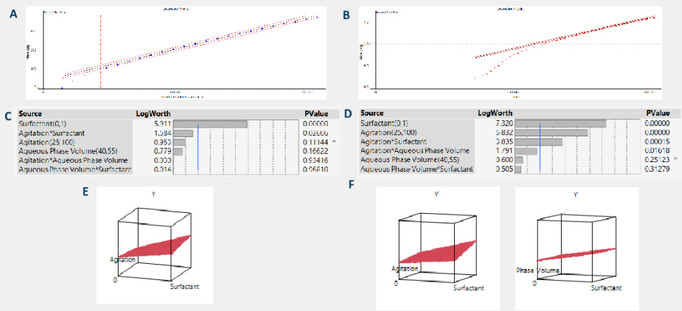


Figure 9. Screen DOE results. (A) Aqueous phase example. (B) Oil phase example. The dissolution rate calculation, parameter significance analysis and, the response surface of significant parameters of the aqueous phase (A, C and E) and the oil phase (B, D and F).

CONCLUSION(S)

The effects of surfactant content, agitation rate and 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 ($P<10^{-5}$) and the interaction between agitation and surfactant content ($P<0.03$) 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 ($P<10^{-5}$), agitation rate ($P<10^{-5}$) and the interactions between 1) surfactant content and agitation rate ($P<0.0002$) and 2) agitation rate and aqueous phase volume ($P<0.02$) were identified as the statistically significant factors on the transfer profile into the oil phase. Generally speaking, increasing surfactant content from 0% to 1% and agitation rate from 25 rpm to 100 rpm increases the permeation rate of drug substance into the oil phase.
- For the aqueous phase, with a fixed agitation rate and dissolution medium volume, the nifedipine drug substance dissolution rate was proportional to the solubility in the aqueous phase, which was in turn proportional to the surfactant content.
- Solubility of nifedipine in Octanol-saturation aqueous phase decreases by 20% - 30%.
- Increasing surfactant content from 0% to 1% decreases nifedipine partition coefficient in the octanol/aqueous system from 1280 to 190.
- The results will be translated in a full sized paddle apparatus in the biphasic dissolution of the nifedipine extended-release tablets for IVIVC establishment.

FUNDING / GRANTS / ENCORE / REFERENCE OR OTHER USE

The work is in part supported by FDA CDER Critical Path Funding CP 17-21.

DISCLAIMER

The contents in this poster reflect the views of the authors and should not be construed to represent FDA's views or policies. The mention of trades names, commercial products, or organizations is for clarification of the methods used and should not be interpreted as an endorsement of a product or manufacturer.

FDA U.S. FOOD & DRUG ADMINISTRATION