Buccal and Sublingual Delivery of Nifedipine
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Purpose
Poor solubility and extensive first-pass metabolism are two major challenges affecting oral drug delivery. Despite the fact that various technologies, for example, amorphous solid dispersions have been employed to overcome the solubility challenge, few of them have addressed the metabolism issue. There is a pressing need to develop formulations that can overcome these two hurdles concurrently.

In this study, we sought to incorporate amorphous technology and/or drug solubilizers in the preparation of orally-dissolving films to overcome the delivery challenges of nifedipine, a poorly soluble drug which undergoes extensive first-pass metabolism.

Accordingly, our objectives were to fabricate and characterize orally-dissolving films of nifedipine and to demonstrate the improved bioavailability of the nifedipine oral film after sublingual or buccal administration relative to a traditional oral route of administration.

Methods
Oral films of nifedipine were prepared by a standard solvent-casting method. The oral films were physically characterized by XRPD, FTIR, etc. The drug content, content uniformity, disintegration and dissolution of the oral films were also determined. Physical stability of the oral films were monitored for up to 28 days. The cytotoxicity of the oral films was determined by using a LDH release assay. Finally, buccal and sublingual delivery of the nifedipine oral films were assessed in rabbits.

Results
Our formulation consisted of HPMC, PEG, Tweens and nifedipine. XRPD data indicated that nifedipine remains as amorphous in the films. However, there does not exist significant interaction between the drug and the excipients as revealed by the FTIR study. The drug content was determined to be 101.6±0.023%. The film started to disintegrate within 15 seconds and the disintegration was completed within two minutes. Compared with the crystalline drug, the oral film increased the solubility of nifedipine by 10x, which is attributable to the amorphous nature of the drug. The oral film was determined to be physically stable at low temperature and low humidity condition for at least 28 days. The nifedipine oral film did not show any significant toxicity (paired student t-test, p>0.05) relative to the control. Relative to a traditional oral route of administration, both buccal and sublingual administrations of the oral films, significantly improved the AUC0→24h and AUC0→∞ by 3.9-4.7x, and 3.0-3.8x, respectively, which were determined to be statistically significant (unpaired student t-test, p<0.05). This may be attributable to an enhanced drug solubility and avoidance of first-pass metabolism.

Conclusion
We have developed orally-dissolving films for the delivery of nifedipine. These oral films exhibited fast disintegration and improved the solubility of nifedipine significantly and show negligible cytotoxicity. Upon sublingual or buccal administration, the nifedipine oral films provided fast drug absorption into the systemic circulation and significantly improved the drug exposure in animals relative to a traditional oral route of administration, and this may be attributable to an enhanced solubility and/or avoidance of first-pass metabolism. A future study is warranted to confirm our findings in humans.