Formulation Design Space for Stable, pH Sensitive Crystalline Nifedipine Nanoparticles
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Purpose
Recently, pH sensitive nanoparticles prepared using eudragit (for enteric coating) have been investigated to deliver drugs to the intestine. This promising technique of enteric coating limits drug degradation in the harsh environment of the stomach, shields the stomach from irritant molecules and allows complete drug release at the intestinal pH. Till date, pH sensitive polymeric nanoparticles are prepared without a definite design space for formulation parameters, which may lead to instability issues. This research involves a DoE approach and stability testing to critically investigate formulation parameters and product stability for the preparation of stable, pH sensitive nifedipine nanoparticles (BCS class II drug). Additionally, this study emphasizes stability testing of the optimized formulation for three months (at 4°C, 25°C and 40°C) and in vitro dissolution testing at two different pHs (1.2 and 6.8).

Methods
A novel manufacturing technique “quasi-emulsion solvent diffusion method” was used to prepare pH sensitive nifedipine nanoparticles. Eudragit L100-55 and polyvinyl alcohol (PVA) were used as stabilizers. In order to investigate various formulation parameters for the preparation of pH sensitive nifedipine nanoparticles, a central composite DoE was used. Three factors: 1) PVA concentration (1-10 %w/v); 2) amount of eudragit L100-55 (25-75 mg); and 3) volume of ethanol (1-5 mL) were monitored against responses such as particle size, polydispersity index and surface charge in the pH sensitive crystalline nifedipine nanoparticles. 50 mg eudragit L100-55 was added to 1.5 mL ethanol in an amber vial, 2.5 mg of nifedipine was dissolved in the above solution under stirring at 300 rpm (solution ‘a’). In another 10 mL amber vial, 5 mL of 3 % w/v PVA solution was kept under stirring at 600 rpm (solution ‘b’). Solution ‘a’ was mixed with ‘b’ under probe sonication, following which the mixture immediately converted to a biphasic nano-emulsion. The solution was agitated (350 rpm) at room temperature for 24 h to remove the organic solvent, forming a nanoparticulate suspension. The formulation was protected from light and the entire manufacturing process was carried out at 2-8°C to prevent any drug degradation due to photolytic and thermal stress. In vitro dissolution of the optimized formulations and the neat drug at two different pHs (1.2 and 6.8) were evaluated using USP apparatus II (paddle apparatus). Stability studies were performed at three different conditions: 4°C, 25°C and 40°C. The optimized formulations from the validated DoEs were used for stability studies for 1 and 3 month/s.

Results
Design Expert was used to evaluate the DoE results for the formulation parameters. According to the ANOVA for the formulation parameter DoE, the surface cubic model was significant for the three factors (concentration of PVA, amount of eudragit and volume of ethanol) indicating that the model was significant for the three responses monitored, namely; particle size, PDI and surface charge of the pH sensitive nifedipine nanoparticles. Overall, the particle size was smaller (<250 nm) when the PVA concentration was >3% w/v and the eudragit amount was <55 mg. However, the volume of ethanol had minimal effect on the particle size. PDI was smaller (<0.2) when the PVA concentration was >5% w/v, eudragit amount >40 mg and ethanol volume >2 mL. Surface charge (>4 mV) increased with increase in the PVA concentration (>3 %w/v), the eudragit amount had a little effect on the surface charge. The optimized pH sensitive nifedipine nanoparticles had the following characteristics: mean particle size (131.86±8.21 nm), PDI (0.135±0.008), and surface charge (-7.631±0.146 mV). A significant particle aggregation was observed for the nanoparticle formulation stored at 40°C for three months, however those stored at 25°C and 4°C showed intermediate and no aggregation, respectively. Approximately, 50% depreciation in drug loading was observed for nano-formulations stored at 40°C, compared to the nano-formulations stored at 4°C and 25°C. This may be due to thermal or photolytic degradation of nifedipine. The optimized pH sensitive crystalline nifedipine nanoparticles resulted in: approximately, 70% and 20% drug release at pH 6.8 and 1.2 respectively within 3 h, compared to 9% (pH 6.8) and 6% (pH 1.2) release of macro-crystalline neat drug. The optimized pH sensitive nifedipine nanoparticles resulted in an eight-fold supersaturation level compared to the neat crystalline drug by three hours.

Conclusion
A combination of novel manufacturing technique and an extensive DoE approach were used to critically investigate the formulation parameters that significantly impact the preparation of stable pH sensitive crystalline nifedipine nanoparticles. The optimized formulation showed a long term stability at 4°C, compared to 25°C and 40°C. In vitro dissolution testing showed significant solubility enhancement in nifedipine formulated as pH sensitive nanoparticles.