The purpose of these studies was to develop a palatable, stable, oral liquid dosage form for pediatric use: Lisinopril & Meclizine. The goal was to develop a diluent and study the stability and palatability properties of the formulation. The stability of the drug was studied as a function of pH, temperature, and concentration but meclizine presented solubility issues. Thus the focus of the studies for each drug differed.

For lisinopril, the goal was to develop a diluent and study the stability and palatability properties of the formulation. The mobile phase consisted of 0.03 M monobasic potassium phosphate adjusted to pH 4.1 with phosphoric acid (1:9 vol/vol) with 0.004 M 1-Octanesulfonic acid sodium salt. The flow rate was set to 1.5 mL/min through a C16 Column with UV detection at 215 nm. Retention time was ~4.0 minutes. Fresh standards were prepared on a daily basis to ensure that no other ingredient interfered with the quantization of the API. Before submission of an IND on either drug the stability studies were performed on the selected formulations. The stability of the drug was measured as a function of pH, temperature, and concentration. For the palatability of lisinopril in solution, three trials were identified as successfully masking the product by providing adequate sweetness, flavor, and consistency. The addition of amino acids does not seem to improve the stability of the mixture. A clear palatable solution of meclizine using citric acid, and ethanol containing products should be avoided in pediatric formulations. The pH 4 buffer and alcohol solution were tested. The pH 4 buffer was prepared with deionized water containing 2.5% citric acid and 2.5% ethanol. A 2% Tween 80 solution buffered to pH 4 with citric acid was also evaluated. These solutions were assessed for the presence of particles after 48 hours. Cyclodextrin (1 mol/l) was added to the citric acid buffer solutions and solubility was reassessed after 24 hours. Additional solutions of ethanol/water (5%/95%) and ethanol/phosphate buffer solution (5%/95%) were also tested to determine effects of alcohol on meclizine (1mol/L) solubility. A 2% Tween 80 solution buffered to pH 4 with citric acid was also evaluated. These results were all evaluated after 48 hours.

Results

Discussion

The amount of lisinopril remaining at 210 days at each storage condition is listed in the table below. The average relative standard deviation was 15%. The correlation coefficient for the linear regression was 0.99. For the palatability of lisinopril in solution, three trials were identified as successfully masking the product by providing adequate sweetness, flavor, and consistency. The three trials only differed by flavor (Bubblegum, Grape, and Watermelon) and the ratio was 1:10, lisinopril solution (2 mg/mL in pH 4.75), 10 mL Ora-Sweet, and 10 mL Ora-Plus and 1 drop flavoring. The palatable lisinopril solution was not tested by the HPLC for stability. Initially, the 3:1 w/w mixture to meclizine ratio provided the best solubility results. Following additional mixing, particles of meclizine began to fall out of solution. A pH of 4 was selected based on increased solubility compared to other pH solutions tested. The cyclodextrin mixture was unsuccessful, so other solutions were tested. A solution of ethanol and sterile water resulted in a stable liquid formulation; however, alcohol containing products should be avoided in pediatric preparations. The pH 4 buffer and alcohol solution was selected as the diluent for lisinopril. The addition of amino acids to the cyclodextrin mixture was considered not acceptable. A final solution of Tween 80, the citric acid buffer solution (pH 4) and meclizine (1mg/mL) resulted in a clear and stable formulation following continuous mixing for 3 hours. The concentration of meclizine was increased from 1mg/mL to 2mg/mL following the addition of Tween 80 (2%) while still maintaining a clear solution. The final preparation of citric acid buffer (pH 4), Tween 80 (2%), and meclizine (2mg/mL) were stored at room temperature, 32°C, and 45°C for 182 days. Samples were obtained over this time period and assayed using HPLC to evaluate the stability of the drug. The results were inconclusive due in part to the appearance of a degradant in the samples stored at the higher temperatures.

References