Development of Powder-In-Bottle Formulation of Hydroxyurea with Methylparaben Preservative
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Purpose
To develop a powder-in-bottle (PIB) formulation of hydroxyurea, containing methylparaben as a preservative.

Methods
Hydroxyurea, a chemically hydroxylated derivative of the symmetrical urea is currently under investigation for administration to pediatric patients suffering from sickle cell anemia. The PIB clinical formulation contains sodium benzoate as a preservative and needed to be changed because the commercial syrup diluent has replaced sodium benzoate with methylparaben. A 23 screening factorial design matrix with nine different combinations was used to study the compatibility of methylparaben with hydroxyurea and excipients in open cap storage condition (40°C/75%RH) for 4 weeks. The compatibility of hydroxyurea with excipients in closed cap conditions at 30°C/65%RH and 40°C/75%RH storage for up to 6 weeks was also studied. The nine different hydroxyurea blend combinations were tested for physical appearance, thermal properties (differential scanning calorimetry), pH (blend reconstituted in Humco® simple syrup), moisture content, microbial limit testing (MLT), and antimicrobial effectiveness testing (AET). An HPLC method was developed for assaying hydroxyurea.

Results
The nine formulation blends stressed at 40°C/75%RH with open cap conditions had the following characteristics: (1) absorption of substantial moisture, liquefying by the end of 4 weeks; (2) significant degradation of hydroxyurea by HPLC; (3) pH of the hydroxyurea blends reconstituted in Humco® simple syrup ranged from 3.5 to 6; and (4) shifts in melting point of hydroxyurea. Three selected formulation blends were then stressed at 40°C/75%RH with closed cap conditions and demonstrated (1) significant degradation of hydroxyurea observed in the blend containing the highest concentration of anhydrous citric acid, which also demonstrated a high tendency to absorb moisture and (2) MLT and AET values within the specified limits of USP class 3 products. The results of the open and closed cap compatibility studies under accelerated and ambient storage conditions demonstrated that a formulation blend with 80.32 % w/w of hydroxyurea, 0.67% w/w of methylparaben, 10.98 %w/w of sodium citrate, and 8.03%w/w of citric acid performed the best and is an ideal candidate for the clinical studies.

Conclusion
We have successfully developed an optimized powder-in-bottle formulation for hydroxyurea containing methylparaben as a preservative with acceptable stability and antimicrobial effectiveness.