Preformulation Studies of Artemether, Quinine and Artemether-Lumefantrine Intended for Fixed-Dose Suppository Formulations
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Purpose
To identify critical variables that could affect the formulation and quality attributes of pediatric antimalarial suppositories using solubility studies and solid-state characterization

Methods
Solid state characterization was conducted using a Fourier Transform Infra-Red (FTIR) analysis of the model drugs, excipients (base and surfactant) and their physical mixtures to monitor physical interaction and intra-compatibilities of the model drugs and excipients based on harmonic oscillations of the bending and stretching of bonds. To investigate the thermodynamics of the base-drug mixtures, and the entropy and enthalpy of mixing in the developed suppositories, differential scanning calorimetry (DSC) method was used to study drug-base interactions, molecular dispersion and thermal behavior. From the entropy and enthalpy of mixing values, Flory-Huggins modeling was used to determine the interaction factor (X) on how favorable is the mixing of the base and drugs, and to predict possibility of crystallization of the drug in the suppositories. Solubility of the model drugs was carried out to determine the extent of solubility of the model drugs in different media - phosphate buffer, pH 7.2 (intended as dissolution medium) and distilled water, within 24 hours.

Results
Characteristic FTIR peaks of Artemether (2873.8 cm–1 and 2845.1 cm–1 due to C-H stretching vibrations), Quinine (718.1 cm–1 and 1079.4 cm–1 due to C-H deformation and methoxy C-O stretching) and Lumefantrine (1465.3 cm-1 and 1485.9 cm-1 due to C-H bending) were retained in the FTIR spectra of the physical mixtures of the drugs and the excipients. Characteristic DSC onset-of melting point endothermic values of 87.330C and 177.180C for artemether and quinine respectively were slightly modified to 86.790C and 172.430C in the DSC thermograms of the model drugs and the bases. The Flory-Huggins interaction factor (X) from the thermal study had values of 0.001 for the drug: base ratio (1:1 and 1:3) with the highest value of 0.163 obtained for the drug: base ratio (3:1). These values indicated favoured thermodynamic mixing and thermodynamic stability of the drug and base. There was a gradual increase in solubility of the drugs within 24 hours with more solubility noticed in the phosphate buffer, thus favoring the alkaline rectal environment where suppositories are administered. The solubility of artemether was enhanced in the fixed-dose mixture, while quinine showed no significant difference in both media. The enhancement in solubility is important since artemether, lumefantrine are Biopharmaceutics Classification (BCS) Class IV drugs and quinine, a BCS Class II drug has borderline solubility.

Conclusion
FTIR showed no drug-excipient interaction. Flory Huggins model indicated drug-base ratio greater than 3:1 could lead to crystallization. Solubility of the drugs was favored in the intended dissolution medium, phosphate buffer, compared to distilled water.