Sulfobutylether-β-Cyclodextrin (SBE-β-CD) Fisetin Complex Dry Powder Formulation for Lung Delivery
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Purpose
This study aims to increase the aqueous solubility of a hydrophobic flavonoid, fisetin, by complexing the compound with sulfobutylether-β-cyclodextrin (SBE-β-CD). The complex is then to be spray dried and characterized to produce a dry powder that is suitable for inhalation purpose.

Methods
A screening process was carried out for fisetin in three different types of cyclodextrins, namely β-cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD) and SBE-β-CD. Consequently, phase solubility profiles of fisetin in the three types of cyclodextrin were plotted. The 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay was conducted on all complexes to evaluate their antioxidant activity by determining the 50% inhibition concentration (IC50) value. The SBE-β-CD fisetin complex was further studied, with and without inclusion of ethanol in formulations. The complex was spray dried and evaluated using laser diffraction particle sizing and X-ray diffraction (XRD) analysis.

Results
From the phase solubility plot, complexation of fisetin with SBE-β-CD gave the highest complexation efficiency, followed by HP-β-CD and β-CD with values of 0.052, 0.028 and 0.019, respectively. The DPPH assay showed that the IC50 value of the fisetin complexes with SBE-β-CD, HP-β-CD and β-CD were not significantly different (p>0.05) when compared to the drug fisetin, being 3.34 ± 0.11, 3.22 ± 0.04 and 3.56 ± 0.30 μM, respectively and 3.68 ± 0.11 μM for fisetin. Further optimization of the complex in the mixture of ethanol and water increased the percentage of solubilized fisetin in the SBE-β-CD complex from 15.2 ± 1.1 to 90.2 ± 3.9%, compared to using water alone. The spray dried complex powders had volume median diameter between 2 to 5 μm and the XRPD analysis showed that the spray dried powder was in the amorphous form.

Conclusion
This study has shown that complexation of fisetin with SBE-β-CD was able to enhance its solubility while maintaining its antioxidant activity. Spray drying of the complex was possible to produce a powder of size properties appropriate for inhalation purposes, which may be suitable in a pulmonary-targeted therapy of fisetin, such as in acute lung injury or lung cancer.