Development of a capillary electrophoresis method for the chiral purity determination of dexmedetomidine with investigation of the complexation between cyclodextrins and medetomidine enantiomers

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Dexmedetomidine is a selective α2-adrenergic agonist used as a sedative in anesthesia, while its enantiomer levomedetomidine has no sedative effects. A CE method was developed based on a quality by design-based methodology for limit test for the enantiomeric impurity levomedetomidine. The analytical target profile was defined that the method should be able to determine levomedetomidine with acceptable precision and accuracy at the 0.1% level. From initial scouting experiments, sulfated β-cyclodextrin was selected as chiral selector. The selected working conditions were a 21.3/31.5 cm, 50 µm id fused-silica capillary, a 50 mM sodium phosphate buffer, pH 6.5, containing 40 mg/mL sulfated β-cyclodextrin, a capillary temperature of 17°C and an applied voltage of 10 kV. The method demonstrated repeatability and intermediate precision of content and migration time between 9.3 and 4.2% with accuracy in the range of 92.0 and 98.9%.

The enantiomeric migration order was observed in the presence of cyclodextrins with phosphate buffer, pH 2.5, which showed dependence on the cavity size and the substitution pattern of the cyclodextrins. Opposite migration order was observed in the presence of the native selectors: β-cyclodextrin (β-CD) and γ-cyclodextrin (γ-CD) as well as the anionic derivatives: randomly sulfated β-CD (S-β-CD) and heptakis(6-O-sulfo)-β-CD (HS-β-CD). A mechanistic study of the complexation demonstrated that dexmedetomidine formed more stable complexes with β-CD and S-β-CD, while levomedetomidine interacted stronger with γ-CD and HS-β-CD.

Using rotating frame nuclear Overhauser spectroscopy (ROESY) enabled determination of the complex structures of medetomidine enantiomers with β-CD, γ-CD and HS-β-CD. In the case of the native CDs, the phenyl ring of medetomidine entered the cavity through the wider secondary rim of the CDs, whereas the protonated imidazole ring was positioned inside the CD cavity interacting with the sulfate groups of HS-β-CD.