Charge-Transfer Reaction of 1,4-Benzoquinone with Crizotinib: Spectrophotometric Study, Computational Molecular Modeling and Use in Development of Microwell Assay for Crizotinib

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Abstract:

The reaction of 1,4-benzoquinone (BQ) with crizotinib (CZT); a novel drug used for treatment of non-small cell lung cancer) was investigated in different solvents of varying dielectric constants and polarity indexes. The reaction resulted in the formation of a red-colored product. Spectrophotometric investigations confirmed that the reaction proceeded through charge-transfer (CT) complex formation. The molar absorptivity of the complex was found to be linearly correlated with the dielectric constant and polarity index of the solvent; the correlation coefficients were 0.9425 and 0.8340, respectively. The stoichiometric ratio of BQ:CZT was found to be 2:1 and the association constant of the complex was found to be $0.26 \times 10^3 \, \text{L mol}^{-1}$. The kinetics of the reaction was studied; the order of the reaction, rate and rate constant were determined. Computational molecular modeling for the complex between BQ and CZT was conducted, the sites of interaction on CZT molecule were determined, and the mechanism of the reaction was postulated. The reaction was employed as a basis in the development of a novel 96-microwell assay for CZT. The assay limits of detection and quantitation were 5.2 and 15.6 $\mu$g ml$^{-1}$, respectively. The assay was validated as per the guidelines of the International Conference on Harmonization (ICH) and successfully applied to the analysis of CZT in its bulk and capsules with good accuracy and precision. The assay has high throughput and consumes minimum volume of organic solvent thus it reduces the exposures of the analysts to the toxic effects of organic solvents, and significantly reduces the analysis cost.

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