Poster 10

Cyclodextrin inclusion complexes of Palbociclib with enhanced solubility for the treatment of breast cancer

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Purpose

Breast cancer is the second most common cause of cancer-related deaths in women globally. Palbociclib (Pal) is a piperazine pyridopyrimidine drug that is approved by the FDA in combination with an aromatase inhibitor for HR-positive, HER2-negative advanced or metastatic breast cancer. Palbociclib functions as a kinase inhibitor and was the first CDK4/6 inhibitor to be approved. The current treatment is by using a combination therapy due to its low aqueous solubility. In this project, we have used sulfobutylether-β-cyclodextrin (SBECD) to form molecular inclusion complexes with Pal to increase its aqueous solubility and stability. We aim to deliver Pal-CD complexes orally, for enhanced oral bioavailability.

Methods

Pal-CD complex was prepared using the saturated solution method. Phase solubility studies were conducted to evaluate Pal solubilization with increasing CD concentration. Job's plot was constructed to understand the stoichiometric ratio for inclusion complex formation. Solid-state characterization was performed using DSC and FT-IR. Accelerated stability study was evaluated on Pal-CD complexes for 28 days at 40°C and 75%RH. In-vitro Caco-2 monolayer permeability studies were performed to evaluate the impact of formulation on drug transport. In-vitro anticancer efficacy of the complexes was studied in MCF7 breast cancer cell lines using MTT assay.

Results

Phase solubility studies indicated increasing solubility of Pal with increase in SBECD concentration. The highest solubility of Pal was observed in 200 mM SBECD concentration (763.89 µg/ml or 1.71 mM), used for further studies. The complexes were observed to be stable at a stoichiometric ratio of 2:1 (Pal: CD). Pal-CD complexes were observed to be stable after 28 days storage at 40°C and 75%RH. In-vitro permeability studies revealed significant enhancement (1.5-2-fold) in Pal transport across Caco-2 monolayers, when complexed with CD. Pal retained its cytotoxicity, as observed to by in-vitro cytotoxicity studies in MCF7 cells (IC50 value of 3.1±2.7 µM for Pal and 2.9±1.04 µM for Pal-CD complex).

Conclusion

These results substantiate SBECD to be a promising drug delivery carrier for Pal to increase its aqueous solubility. In-vitro cytotoxicity studies indicated appreciable toxicity against breast cancer cells.

Keywords: Breast cancer, triple negative