Preparation and Characterization of Ternary Inclusion Complexes for Solubility Enhancement of Paliperidone

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ABSTRACT SUMMARY

The effect of three hydrophilic polymers, namely, Polyvinylpyrrolidone (PVP), Poloxamer and polyethylene glycol (PEG) on the complexation and solubilizing efficiencies of bata-cyclodextrin (β-CD) was investigated. Paliperidone (PLP), a poorly water soluble drug, was used as a model drug. Phase solubility studies were carried to determine the complexation efficiency of β-CD and polymers. Among various polymers PVP K-30 (0.3% w/v) was selected for ternary solid complexes preparation. Ternary complexes comprising of PLP, β-CD and PVP were prepared and characterized. The significant improvement in aqueous solubility of PLP can be attributed to the enhanced complexation efficiency due to presence of PVP.

EXPERIMENTAL METHODS

Phase solubility studies were carried out as per Higuchi and Connors method to study the inclusion ability of β-CD with PLP. The water soluble polymers viz. PVP, poloxamer and PEG in various concentrations were screened for their effect on solubility enhancement of PLP and inclusion efficiency in presence of β-CD.

The aqueous solubility of PLP was linearly increased as a function of the concentration of β-CD alone and in the presence of hydrophilic polymers. From the study, PVP has shown the highest solubility enhancement in 0.3% w/v concentration among various polymers. Hence, it was taken further for complexation and characterization.

The PLP-β-CD-PVP ternary complexes were prepared by anti-solvent method in 1:1 molar ratios of PLP:β-CD and PVP (0.3% w/v) was added to form a ternary system. The required amounts of β-CD and PVP were dissolved in water and PLP in methanol. This was followed by a gradual addition of drug solution to the aqueous solution of β-CD and PVP. The solution was stirred and the temperature was maintained at about 75°C. The stirring was continued till the solvent is evaporated and product precipitates. The
product was then dried and passed through 80 size sieve with minimum abrasion.

The solid ternary system was characterized by DSC, FT-IR, PXRD, and SEM. The aqueous solubility of the complexes was determined by saturation solubility method in water. In-vitro dissolution studies were performed to study the dissolution properties of PLP in the ternary system. It was carried using USP dissolution apparatus-II (paddle type) in 500 mL phosphate buffer, pH 6.8, at 37 ± 0.2 °C with a paddle rotating at 50 rpm. The amount of PLP dissolved was determined using UV–Vis spectrophotometer at 237 nm.

RESULTS AND DISCUSSION

The aqueous solubility of PLP using β-CD in presence of various hydrophilic polymers (PVP, PEG and poloxamer) at their various concentrations were studied. It was found that the solubility of drug increased significantly with β-CD alone (binary system) or in presence of various polymers (ternary system) due to inclusion complexation. In the phase solubility study of ternary system it was found that, 0.3% w/v of PVP K-30 showed maximum solubility enhancement of PLP. Hence, it was taken for preparation of ternary complexes. Phase solubility study curve was found to be of A_L type for PLP:β-CD and PLP:β-CD:PVP systems suggesting increase in solubility of drug as a function of cyclodextrin concentration alone and in presence of PVP.

The aqueous solubility of PLP in ternary complexes (PLP: β-CD: PVP) was found to be increased by 30 folds in comparison to the binary system with β-CD alone (14 folds). In-vitro studies showed that the dissolution rate of drug was significantly improved by complexation with β-CD in presence of 0.3 % w/v PVP with respect to the drug alone. The dissolution study revealed that >90% of drug was released from ternary complexes in 30 min, while the release of pure drug was <30 % at the same time interval. The characterization of ternary system using DSC, PXRD, SEM and FTIR also suggested formation of ternary solid complexes between PLP, β-CD and PVP.

CONCLUSION

As evident from the results, it can be suggested that ternary complexation can be effectively used as a novel approach for solubility and dissolution enhancement of paliperidone.

REFERENCES


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