Abstract

The combination of Atorvastatin calcium (AT) (10.28mg equivalent to Atorvastatin 10mg), Fenofibrate (FE) (160mg) and Ezetimibe (EZ) (10mg) are used to improve mixed dyslipidemia. They are poorly water soluble drugs. The objective of the study was to enhance the solubility and therefore bioavailability of AT, FE and EZ using complexation with β-Cyclodextrin (β-CD). The complexation of β-CD with AT, FE and EZ in combination was prepared by Co-Evaporation technique. With Co-Evaporation technique, the crystal form of AT, FE and EZ were changed to amorphous form and appeared to be associated with better performance in apparent solubility, dissolution and pharmacokinetic studies, compared with market formulation. Oral AUC_{0-24h} values in male Wistar rats for marketed and co-evaporated AT, FE, EZ were as follow: 2644.9 ± 718.5 ng h/ml, 942.3 ± 177.9 µg h/ml and 302.8 ± 83.2 ng h/ml for marketed AT, FE and EZ, respectively and 6708.4 ± 1241.6 ng h/ml, 1959.9 ± 450.3 µg h/ml and 725.6 ± 122.5 ng h/ml for co-evaporated complex of AT, FE and EZ, respectively. The AUCs of co-evaporated complex of AT, FE and EZ significantly increased (P < 0.01) compared with marketed one, suggesting that the enhanced bioavailability was attributed to amorphous nature and solubilization effect of β-CD. In addition, C_{max} values of marketed AT, FE and EZ was 774.9±69.4 ng, 133.6 ± 20.6 µg and 52.6 ± 7.4 ng, respectively whereas C_{max} value of co-evaporated complex of AT, FE and EZ was 1595.4 ± 129.5 ng, 317.6 ±48.9 µg and 101.6 ±12.6 ng, respectively. The C_{max} of co-evaporated complex significantly increased (P < 0.01) compared with marketed one, suggesting that the higher exposure of drug was attributed to amorphous nature and solubilization effect of β-CD. It was concluded that enhancement of solubility and therefore bioavailability of AT, FE and EZ in combination could be achieved by Co-Evaporation method of complexation with β-CD. The reduction of amount of β-CD for complexation could be achieved. The reduction of dose of AT, FE and EZ therefore their side effects could be reduced by Co-Evaporation method.

Keywords

Atorvastatin, Fenofibrate, Ezetimibe, Bioavailability, β-cyclodextrin, Co-Evaporation