

## ABSTRACT

The deficiency of vitamin D is a global concern affecting individuals of all age groups. Cholecalciferol (vitamin D<sub>3</sub>) is a lipophilic crystalline molecule and it is highly susceptible to degradation under environmental conditions including light, temperature, and oxygen, and its degradation rate is high in the low pH range, therefore drug delivery-based approaches should be explored for its optimum effect. In the present research work, in the first approach, enteric solid dispersion of cholecalciferol was developed using hydroxypropylmethylcellulose acetate succinate (HPMCAS) by solvent evaporation method. The enteric solid dispersion of cholecalciferol was characterized by FTIR, DSC, SEM, and XRD, and these techniques indicated the successful formation of the enteric solid dispersion-based products. The spectral analysis indicates that the characteristics functional group of the solid dispersion formulation had almost the same features as that of native drug and polymer physical mixture. The study indicates that molecular interactions did not occur, ruling out the possibility of alteration in the chemical structure of the active molecule. The SEM study revealed the crystalline form of cholecalciferol with irregular orthorhombic crystals. However, the solid dispersion formulation of cholecalciferol appeared to be small aggregates of amorphous particles. The morphological changes in the particles thus indicate the formation of a new solid phase, correlated with the changes in the crystalline state, leading to a single amorphous phase. The thermal behaviour of cholecalciferol can be witnessed by a sharp endothermic peak characteristic of its crystalline structure as seen under the SEM. On the other hand, the solid dispersion formulation did not show any endothermic peak event corresponding to the melting of cholecalciferol indicating the formation of solid dispersion. X-ray diffractograms of cholecalciferol exhibited peaks attributed to its crystalline characteristics. On the other hand, in the solid dispersion formulation, the characteristics peaks of cholecalciferol were not appeared. This could be attributed to the conversion of cholecalciferol in amorphous or molecular dispersion form in the solid dispersion formulations. Solid dispersion formulation in this study comprises cholecalciferol, polymer and surfactant. Hence, the safety profile of the formulation in terms of cytotoxic potential in Caco-2 cells was investigated. The results indicated that the polymer/surfactant used in the enteric solid dispersion formulation of cholecalciferol had no cytotoxic effect on Caco-2 cells. Subsequently, the dissolution behaviour of cholecalciferol was studied using two-stage dissolution in a biomimetic medium comprising simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). The study indicated pH-dependent release profile and improved dissolution of cholecalciferol from enteric solid dispersion-based

products. The developed enteric formulation of cholecalciferol also showed higher relative bioavailability as compared to native molecule. Finally, the stability study indicated no significant changes in the cholecalciferol content in the developed formulations under the experimental conditions. The developed enteric solid dispersion for cholecalciferol exhibited potential for further translational studies. In the second approach, PVP-K30 based solid dispersion of cholecalciferol was developed and encapsulated in delayed release hydroxypropylmethyl cellulose (HPMC) capsule (DRHCap-SD). The solid dispersion of cholecalciferol was characterized by FTIR, SEM, DSC and X-ray diffraction analysis, and these techniques indicated the successful formation of the solid dispersion of cholecalciferol. Also, solid dispersion formulation exhibited no cytotoxic effect on Caco-2 cells. The dissolution study of DRHCap-SD and SD formulation of cholecalciferol in SGF and SIF medium demonstrated improved dissolution of cholecalciferol from DRHCap-SD formulation. The storage stability study demonstrated no significant changes in the cholecalciferol content in the DRHCap-SD formulations. In the third approach, self-emulsifying drug delivery system (SEDDS) based formulation for cholecalciferol delivery was prepared using oil, surfactant and co-surfactant. The cholecalciferol loaded SEDDS formulations were characterized on the basis of different parameters including emulsification tendency, precipitation of drug, phase separation, density of globules and globules uniformity. The morphology of the SEDDS formulation was investigated by transmission electron microscopy (TEM). The size, zeta potential and the polydispersity of the formulation was determined using the zeta sizer. The SEDD formulation exhibited size in nanometre range with narrow particle size distribution. The SEDD formulation was subjected to in-vitro stability assessment in SGF and SIF. There were no coalescence, precipitation or phase separations in the formulation. Subsequently, dissolution profile of cholecalciferol SEDDS formulation was studied in SGF (pH 1.2), wherein, formulation exhibited significantly improved dissolution profile of cholecalciferol compared to the native molecule. Developed formulation had no toxic effects on the caco-2 cells and showed improved bio-accessibility, and stability profile. In summary, the formulation strategies explored in this research work exhibited potential for improved oral delivery of cholecalciferol.