ABSTRACT

Introduction: Poorly soluble drugs are slowly absorbed after oral administration as compared with drugs having higher solubility. Consequently, these drugs present a great challenge to further development into bioavailable dosage forms. A critical factor that needs to be considered, therefore, is the performance of the drug in formulations during therapy. The performance of a drug in turn is a function of its physicochemical properties, such as aqueous solubility and drug stability. Hence it is important to enhance the aqueous solubility, dissolution rate and bioavailability of these drugs from its oral solid dosage forms. Solid dispersion technique and cyclodextrin complexation have been used as effective methods to improve the dissolution properties and bioavailability of poorly water-soluble drugs. The present study has demonstrated the possibility of improving dissolution performance of nevirapine (NVP), a poorly soluble drug by solid dispersion technique and also complexation with cyclodextrins (CDs).

Objective: NVP is an antiretroviral drug approved by the FDA and currently used in the treatment of human immunodeficiency virus type 1 (HIV-1) infections. It is one of the most prescribed antiretroviral drug in the developing world, both to prevent vertical transmission and in combination therapy. However, major drawback in the therapeutic application and efficacy of NVP as oral dosage forms is its low aqueous solubility because of its hydrophobic nature. The drug belongs to biopharmaceutical classification system (BCS) class II (low solubility, high permeability) and thus gives rise to difficulties in the formulation of dosage forms and leads to variable dissolution rates with a resultant decrease in oral bioavailability. Therefore, a favourable
formulation which can enhance solubility and dissolution rate of this model drug may help effectively in the therapeutic area of HIV prevention and treatment. Thus in the present investigation, we carried out studies to improve the solubility and \textit{in vitro} bioavailability of poorly soluble drug NVP through solid dispersion technique using dextran (DEX) fraction (Mw.100,000 Daltons) as a novel carrier and also inclusion complexation with $\beta$-cyclodextrin (βCD) and its derivative hydroxypropyl $\beta$-cyclodextrin (HPβCD).

\textbf{Methods:} Solid dispersions of (SDs) of nevirapine were prepared using a dextran fraction in two different ratio of drug and carrier (3:1 and 1:1 w/w) by three methods i.e., kneading, microwave irradiation and freeze drying method. Similarly, solid binary systems of nevirapine with βCD and HPβCD (1:1M and 1:2M) were prepared by four methods such as kneading, solvent evaporation, microwave irradiation and freeze drying methods. Characterization of prepared SDs and solid binary systems of NVP in solution state was made by drug content estimation, phase solubility studies, saturation solubility studies, $^1$H NMR spectroscopic studies and \textit{in vitro} dissolution studies. Characterization in solid state was done by various analytical techniques such as FT-IR, XRD and DSC studies. Morphological features of the SDs and solid binary systems of NVP with both the CDs were examined by scanning electron microscopy. \textit{In vitro} dissolution studies of pure NVP, physical mixtures (PMs), SDs and solid binary systems were carried out in 900 ml of 0.1N HCl using a USPXXIV type 2-dissolution rate test apparatus by the powder dispersed amount method. The \textit{in vitro} results were computed by using dissolution software PCP DISSO V.3. Dissolution profiles of all SDs and solid binary systems were analysed according to Hixson-Crowell’s cube root law and first order kinetics. Significant differences in the means of dissolution efficiency (DE$_{30}$) values of pure NVP, PMs, SDs and solid binary
systems were tested at 95% confidence with ‘One-way ANOVA’ using Dunnett multiple comparison test.

**Results:** All SDs and solid binary systems of NVP were found free flowing. The low standard deviation (SD) and coefficient of variation (CV) values in drug content estimation indicated uniform drug distribution in all prepared batches. The saturation solubility studies of SDs and solid binary systems showed substantial enhancement of solubility as compared to pure drug alone. The phase solubility studies of NVP with βCD and HPβCD indicated the formation of 1:1 stoichiometric complex with respect to βCD and HPβCD concentrations. The FT-IR studies of SDs with dextran (DEX) and solid binary systems with βCD and HPβCD suggested the possibility of intermolecular hydrogen bonding between sites of NVP and the hydroxyl group of carriers. Changes in proton chemical shift values of NVP in SDs and solid binary systems supports the above possible interaction between NVP and the carriers. DSC studies exhibited the decrease in melting enthalpy (ΔH) values in all prepared batches and indicated the decrease in crystallinity or partial change in crystal form of the drug. The XRD results of all SDs and solid binary systems suggested that no alteration in the crystal structure of NVP, but the crystallinity being modified and reduced to a considerable extent. All SEM photographs of SDs and solid binary systems of NVP revealed the interaction between the drug and carriers in solid state. The dissolution rate of NVP was significantly improved after preparing its SDs with DEX and solid binary systems with both CDs compared to NVP alone. The DE$_{30}$ and DE$_{60}$ values of the SDs and solid binary systems were relatively high (P < 0.01) compared to the values from the PMs and NVP alone. Further, the DE$_{30}$ and DE$_{60}$ values of SDs with DEX and solid binary systems with both CDs prepared by freeze drying method were higher (P < 0.01) than those prepared by other methods. The release pattern in pure
NVP, PMs, SDs and solid binary systems were found to be first order (best fit model) and then followed Hixson-Crowell’s cube root model.

**Conclusions:** The overall study demonstrated the feasibility of preparing SDs of NVP with low molecular weight DEX fraction as a novel carrier and also solid binary systems with βCD and HPβCD to improve the solubility and dissolution rate of the model drug. Hence, the study strongly recommends that developed SDs of NVP with dextran and solid binary systems with both CDs can be further utilised for the formulation of suitable dosage form such as tablets. Further, the drastic increase in the aqueous solubility of NVP afforded by the ‘solid dispersion technique’ and ‘inclusion complexation’ approaches will enable new formulation technologies to be tested in the development of new more effective anti-HIV products.