ABSTRACT

Human Immunodeficiency Virus (HIV) is a retrovirus that causes irreversible destruction of the immune system, leading to the occurrence of opportunistic infections and malignancies. Most of the antiretroviral drugs bear some significant drawbacks such as relatively short half-life, low bioavailability, poor permeability and undesirable side effects. Efforts have been made to design drug delivery systems for anti-HIV agents to reduce the dosing frequency, to increase the bioavailability and decrease the degradation/metabolism in the gastrointestinal tract, and to deliver them to the target cells selectively with minimal side effects. Today, we also have controlled-release systems designed to produce more reliable absorption and to improve bioavailability and efficiency of drug delivery. Usually conventional dosage forms produce wide-ranging fluctuation in drug concentration in the bloodstream and tissue with consequent undesirable toxicity and poor efficiency. This factor, as well as factors such as repetitive dosing and unpredictable absorption, led to the concept of controlled drug delivery system. Keeping those all above parameters, the three drugs i.e., Lamivudine and Emtricitabine alone and in combination with Tenofovir DF were selected for this present study. The dosage forms designed for the selected drugs were matrix tablets by embedment technique, compression coated tablets and microcapsules assisted bilayered tablets with an objective of providing maximum benefit to HIV patients.

The UV method was used for the estimation of Lamivudine, Emtricitabine and Tenofovir DF in individual dosage forms and the HPLC method was used for simultaneous estimation of Lamivudine with Tenofovir DF and Emtricitabine with Tenofovir DF in combination dosage forms and also for the estimation of Lamivudine and Emtricitabine individually in biological samples. The validation of developed HPLC methods was performed. All the three drugs were subjected to the preformulation studies like solubility, partition coefficient, melting point, loss on drying and flow properties. Purification and characterization of selected natural gums was carried out. The controlled release formulations of Lamivudine and Emtricitabine were designed in the form of matrix tablets by embedment technique and compression coating technique respectively. The combinations of Lamivudine with Tenofovir DF, Emtricitabine with Tenofovir DF were formulated in the form of microcapsules assisted bilayered tablets.
The proposed UV and HPLC methods were found to be suitable for the estimation of Lamivudine, Emtricitabine & Tenofovir DF contents in the assay and dissolution samples and biological samples of the formulations. All the drugs were white to off-white in color, odorless and bitter to taste. The solubility of three drugs was decreased upon pH increased. The melting point, LOD results were complying with the pharmacopoeial specifications. Lamivudine had good flowability whereas Emtricitabine and Tenofovir DF showed very poor flowability. The drugs were compatible with all the selected excipients based on IR spectral and DSC studies.

The Lamivudine CR matrix tablets by embedment technique using natural gums and Emtricitabine CR tablets by compression coating technology by varying amounts of coating granules were successfully formulated. The granules of all formulations were found to have good flowability and packageability and were suitable for compression. The tablets of all formulations were found to have enough strength by hardness, tensile strength and friability results. The drug content estimation values reflect good uniformity of the mixing of the drug with excipients during the tabletting process. The wetting time was influenced significantly by the concentration of natural gums. The influence of concentration of gums on drug release rate constant was found to be significant at $P < 0.01$ and the influence of type of gum was found to be significant at $P < 0.1$. The matrix tablets of formulation LET10 prepared by embedment technique showed greater control in drug release (upto 18 hrs) than those prepared by wet granulation of same formula. The embedment technique was found to be more effective for the efficient incorporation of drug in the polymer matrix than wet granulation technique for the preparation of controlled release formulations. The release rate of the Emtricitabine from the compression coated tablet was found to be influenced by the amount of coat thickness at $P < 0.001$ significant level, and also by the composition of the coat at $P < 0.05$ significant level. The compression coated tablets of formulations ECT13 & ECT14 showed greater control in drug release (upto 18 hrs) than other formulations. The drug release from the LET/ECT was found to follow zero order kinetics with anomalous diffusion as release mechanism.

TIR19 contained SSG at 4%w/w and PVP K30 at 1%w/w was considered to be optimum. In the case of microcapsules, at higher concentration of polymer phase, temperature was required for the rigidization of the microcapsules after formation.
Swelling capacity of microcapsules was found to be reduced upon increase in the concentration of polymer. From the percentage yield and entrapment efficiency studies, it was observed that emulsion solvent evaporation method was found to be more successful. The microcapsules prepared by Eudragit showed rough texture, porous and tortuous where as microcapsules prepared by Ethyl cellulose showed continuous texture with no observed porosity. The drug release was more controlled from the microcapsules prepared with Ethyl Cellulose than those prepared with Eudragit RS PO. The drug release rates of both the drugs from their microcapsules were found to be reduced upon increase in the concentration of the polymer and followed zero order kinetics with anomalous diffusion as release mechanism. It was found that the drug release rate was more controlled upon increase in the molecular weight of the polymer, as in the case of Ethyl Cellulose. Though LMC9/EMC9 (1:2 drug polymer ratio) showed similar control in release to that of LMC11/EMC11 (1:1 drug polymer ratio), the later was optimized as it contained less amount of polymer. The bilayered tablets of LT & ET were formulated by considering the optimized formulation of microcapsules of LAM/EMT i.e. LMC11/EMC11 and the immediate release tablet of TDF i.e. TIR19 compressed together into tablets. The bilayered tablets also showed good physical characteristics, which are hardness, tensile strength and friability. The controlled release layer of bilayered tablets showed similar drug release as that of microcapsules before compression but with some less release rate constant. All the optimized formulations (LET10, ECT14, TIR19, LMC11, EMC11, LT & ET) were found to be quiet stable after stability studies at 40 ± 2 °C / 75 ± 5 % RH for a period of 3 months. The overall C_{max}, T_{max}, AUC_{0-t} and K_{el} were completely different between test and reference formulations indicated the successful development of controlled release formulations of both Lamivudine and Emtricitabine. Thus the major objectives of the present investigation were successfully achieved.