Chapter – 7

SUMMARY, CONCLUSION AND RECOMMENDATIONS
SUMMARY AND CONCLUSIONS

The objective of this research work was, formulation development and evaluation of controlled release formulations of antiretroviral drugs, Emtricitabine and Lamivudine alone and combination with Tenofovir DF.

Studies have been carried out on formulation development and evaluation of Lamivudine matrix tablets by embedment technique for controlled release. The literature review on sustained/controlled release formulations of Lamivudine indicated that matrix tablets by embedment technique using hydrophilic and hydrophobic polymers were not reported. Hence the research was undertaken to study the effectiveness of the embedment technique in the preparation of Lamivudine CR tablets by employing natural gums as release retarding polymers.

The Emtricitabine was formulated into compression coated tablets for controlled release. The literature review on sustained/controlled release formulations of Emtricitabine indicated that compression coated tablets using hydrophilic and hydrophobic polymers were not reported. Hence the research was undertaken to prepare the tablets with varying amount of coating granules so as to obtain the tablets of the varied thickness of coating layer to study the effect of coating thickness on the release rate of the drug.

The combination of Lamivudine with Tenofovir DF and Emtricitabine with Tenofovir DF were formulated into bilayered tablets using Lamivudine/Emtricitabine for controlled release and Tenofovir DF for immediate release. The controlled release layer was composed of microcapsules of the respective drug (Lamivudine or Emtricitabine) and the immediate release layer of Tenofovir DF was composed of granules prepared by traditional wet granulation method. Then, the two layers were optimized individually and best formulations obtained were considered for the final bilayered tablet.

Initially, the immediate release tablets of TDF were prepared by wet granulation method. The tablets were prepared in two batches as batch 3.1A contains starch as disintegrant and batch 3.1B contains SSG as a disintegrant. Later, the Lamivudine & Emtricitabine microcapsules were prepared by using emulsion solvent evaporation method by employing Eudragit RLPO, Eudragit RSPO, ethyl cellulose N50 and ethyl cellulose N100 polymers, were studied for their influence at three different drugs to polymer ratios i.e. 1:0.5, 1:1 and 1:2.
Finally, the bilayered tablets of LT & ET were formulated by taking optimized microcapsule formulation of Lamivudine / Emtricitabine and the immediate release granules of Tenofovir DF compressed together into bilayered tablets using multi-station rotary bilayer tablet press.

The following conclusions were drawn from the experimental results

- It was found that the three drugs were efficiently analyzed spectrophotometrically (UV) using water, 0.1N HCl and phosphate buffer pH 6.8 as solvents at their respective $\lambda_{\text{max}}$ (maximum wavelength).
- It was found that the combinations of drugs (LT & ET), drugs in biological sample (rabbit plasma) were efficiently analyzed by using HPLC.
- The solubility of the drugs 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 purification, physiochemical and phytochemical screening of selected three natural gums were successfully carried out.
- 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 $P < 0.1$. 

223
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.

The Lamivudine and Emtricitabine CR microcapsules by emulsion solvent evaporation method using various polymers at different drug polymer ratios were successfully formulated.

The microcapsules of all formulations were found to have moderate flowability and were suitable for compression.

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 Eudragits.

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\text{max}, T\text{max}, AUC\text{0-t} and K\text{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 achieved and the results were appropriately placed.

**RECOMMENDATIONS:**

These experimental findings suggested that this research work can be extended to

- Pharmacokinetic studies of bilayered tablets of LT & ET
- Pharmacodynamic investigations.
- *In vitro – in vivo* correlation studies.
- Selection of suitable packaging.
- Stability studies in their final packing.