CHAPTER 7
SUMMARY
Venlafaxine hydrochloride is a novel antidepressant for oral administration. The short biological half-life (5 ± 2 hrs) and the fast clearance make the drug, a suitable candidate for the development of once a day formulation. Formulation of controlled release dosage form improves patient compliance as well as reduces side effects like nausea and vomiting.

Venlafaxine HCl is having high aqueous solubility (572 mg/mL) and hence it is difficult to formulate sustained release tablets. Effexor® XR capsules by Wyeth Pharmaceuticals are available in the US market. These capsules contain spheroids coated with water insoluble polymer. The capsules were used as reference product and sustained release tablets were prepared with similar dissolution in vitro. Few patents mention the use of cellulose ether along with microbial polysaccharide or coating of spheroids with water insoluble polymer like ethyl cellulose to sustain the release of venlafaxine HCl. In the present study monolithic matrix tablets were prepared such that the formulations are not infringing the patents, cost effective, easy to formulate and are comparable in vitro to the reference products.

Hypromellose and polyethylene oxide were used separately as monolithic matrixing agent for formulation of tablet, a simplest dosage form. Uncoated monolithic tablets failed to give desirable drug release profile due high aqueous solubility of drug. The matrix tablets coated with low viscosity grade of ethyl cellulose and hypromellose prevented burst drug release. Thus developed coated formulation showed comparable drug release to the reference product.

Triple layer tablets were also formulated using hydrophilic polymers in barrier layer and in middle layer. Lactose monohydrate was added as pore forming diluent. The main reason for prevention of burst drug release in triple layer tablets was reduction in surface area of tablet exposed to the dissolution medium.

The developed coated and triple layer tablets showed pH independent drug release and the dissolution pattern was unaltered in presence of 10% ethanolic solution. Dissolution
study in aqueous ethanol indicates that dose dumping will not take place if alcoholic beverages are consumed by patients. FDA requires dissolution data in aqueous alcohol for sustained release formulations.

The drug release was explained by Weibull model. The use of unified Weibull equation is demonstrated to investigate the influence of minor changes in the formulation. FDA can be convinced easily during inspection. Simplex lattice design was used for optimization. The use of radar diagram was explored for comparison of dissolution profile of test formulation with reference product. The reduced amount of polymer was required to formulate triple layer tablets compared to film coated tablets. High productivity triple layer tablets compression machine are available in the Indian market and hence it is cost effective to formulate multilayer tablets to sustain the drug release.

Xanthan gum is a natural carbohydrate. Xanthan gum swells in gastric fluid to produce a highly viscous layer around the tablet through which the drug can diffuse. Triple layer tablets of venlafaxine HCl with three strengths (150, 75 and 37.5 mg) were prepared using xanthan gum. The granules used in the middle layer were identical in the tablets.

The generic formulation development can be hastened by systematic development of different strengths. Bio waver can be granted for lower strengths by FDA.

The two approaches were successfully explored in the current study. The first approach involved the use of barrier membrane coating with pore formers onto a hydrophilic matrix tablet, while the other approach involved the preparation of triple layered matrix tablets. This study demonstrate that stained release formulation of venlafaxine HCl can be developed using different hydrophilic release retardants which released drug slowly over period of 24 hours using systematic formulation approach.