Chapter 9

Summary & Conclusions......
9.1. AN OVERVIEW

Awareness of disease and efforts to gain control over the disease contributed in considerable increase of human life expectancy (25-30 years for the young generation). Life-style drugs improved the quality of life and human performance. All this was possible as the insight to understand disease and its manifestation at cellular and molecular level with advanced technique that were developed in biomedical field and the ability of Pharma-industry to mass produce quality medicines and cheaper prices.

The concept of novel therapeutics i.e., novel drug delivery systems (NDDS) capable of modifying the rate of drug delivery, altering the duration of action and or targeting the delivery of drug to the tissue are seeking wider acceptance in medical fraternity against the conventional dosage forms that delivers drug which is immediately available for action or absorption without any mechanism being incorporated in the system to have spatial or temporal control over drug release, due to enhanced therapeutic efficacy.

Novel Drug Delivery Systems involves use of new or existing drugs presented in newer forms of delivery. The definition normally includes use of new routes of administration different from the originally accepted ones. The designing and development of such delivery systems involve technological advances. These delivery systems are aimed at altering solubility, improving stability or altering bioavailability. The design and change in process builds in cost of the product. Efforts should be made in reducing the cost of production of NDDS so that the total disease management cost is reduced thereby rendeing economic merit to the patient.
9.2. CHAPTER 1. PHARMATECH INDUSTRY

It takes a review of the constrained pharmaceutical industry in terms of (i) business, product(s) and sale; (ii) survival and growth strategies, (iii) patent issues — all having implications on their own and to the people. Indian Pharmaceutical Industry is known for its internationally accepted quality products and cost wise the most efficient, in the world. However, Indian share in the global drug industry is very low, less than 2%. With giant mergers with Indian Pharma Companies, this figure is likely to change under the product patent regime.

Over a year now, there has been lot of apprehensions on the Product Patent which is effective from Jan 2005, as India became signatory to GATT and bound to TRIPS. Opinion expressed by (i) socio-economic experts, (ii) government representatives, and (iii) people have been complied. The 3rd Amendment Patent Bill was passed in the Parliament on March 22nd, 2005. India showed its strength by expressing its will to continue to supply cheaper medicines to industrially underdeveloped countries, especially for AIDS victims. There is a general opinion that these changes in the Bill have been well addressed and protected with end note to ‘wait and watch’ especially if the cost of the medicine would escalate beyond affordability.

9.3. CHAPTER 2. A SURVEY IN HYPERTENSIVE

9.3.1. Hypertension – Life style disease or ageing symptom

Mental stress — an unwanted supplement gift and blessings of modern life, is being looked as the cause of many diseases. This concept needs to be discriminatively analyzed against the short span of life our ancestors who did not live long due to lack of developed immunity against diseases (vaccines), way of fighting out with infections (antibiotics), unavailability of sophisticated and high-tech medical services (surgeries and transplants), malnourishment, social instability (wars) etc. They did not live long
that the aging symptoms/manifestation of body, especially like hypertension could be clinically detected – in light of limited resources and progress in science. With constant intensive need based research and development in science, technology, and socio-economic policies made medical facilities and medicines available to all. This contributed significantly in the health and well-being of human civilization. However, aging symptoms like hypertension and the complications associated with it (which each one has to live with age) has added another challenge; more so when the patient fails to comply with the drug therapy, as one has to comply for the rest of one's life, once developed (in most or almost all the cases). The two main reasons for non-compliance for drug therapy are (1) cost and (2) drug therapy regime.

9.3.2. Conclusions of Questionnaire Results

A questionnaire study was designed and undertaken in an attempt to study the attitudial approach to hypertension and non-compliance to drug therapy. The study was performed on a small population in a limited geographical area (Jhansi), so cannot be a general finding. However, the study results were in line to the reports made by others. Following conclusions could be drawn.

i. Higher ratio of male: female (2.3: 1) undergoing medical check-up.

ii. Majority (~63%) of patients reacted in dismay for they being hypertensive.

iii. Salt and Smoking Control: Amongst the hypertensive, ~82% females and ~77% males were controlling their salt intake. ~24% of men who were smoking and drinking kept a check on their habit.

iv. Nature of Diet and Physical Activity: ~61% females were vegetarian, ~41% of the total study group indulged in walking.

v. Compliance to drug therapy: It was poor. Only ~40% male and ~26% females were regularly taking their medication. The major reason for
non-compliance was their perception to disease and cost. ~57%
simply discontinued their medication, randomly, on and off while ~31%
due to frequency of dosing who felt it ideal if were prescribed once per
day.

vi Side effects: Headache was the most common complaint followed
by dizziness.

vii Overweight: Only ~6% were overweight.

9.3.3. Some Interesting findings

- A awareness to hypertension was higher in females (2.3 times) when the
  literacy rate in men is higher than women.

- Women folk showed better compliance to (i) drug therapy and (ii) non-
  medicinal means of controlling the BP – in terms of salt intake, diet etc.

- In general, patients' complaint of headache with medication.

9.4.  CHAPTER 3. MARKETED METOPROLOL TABLET EVALUATION

9.4.1. Inspiration and Study Relevance

The results of the survey prompted to evaluate metoprolol tartrate tablets available in
market in terms of quality and cost. As the generic products are expected to qualify
the Tests, so were our results as anticipated. However, the cost factors worked out
for different brand showed considerable difference.

The Indian government has initiated its moves to appeal medical community to
practice prescribing active drug rather go brands names, so that the patient is at
discretion to opt for cheaper bio-equivalents i.e., generic version. However, until the
population is educated for this, the process would simply shift from Doctors's table to
Pharmacist's counter. Government's thought of opening “Government Pharmacy
Outlets” for essential drugs to make medicines available at controlled prices in line with the “Government Ration Shops” is a better option to initiate with.

9.4.2. Study Result Conclusions

9.4.2.i. Official and unofficial evaluation

All the tablets under study where within the limits of official specifications in terms of (i) weight variation, (ii) content uniformity, (iii) disintegration test and (iv) drug dissolution. Besides, the requisite tablet organoleptic properties were satisfactory. Therefore, form the from the performed laboratory test data, it can be concluded that all the products were therapeutically bioequivalent. However, tablet coded IR-D had little higher range in which these values fluctuated widely as compared to other tablets.

9.4.2.ii. Comparative Cost Therapy

There is considerable cost variation (~44%) between the tablets. So, prescription of cheaper brand could be taken advantage for and in the interested of patient.

9.5. CHAPTER 4. INTRODUCTION

The present research work deals with the general aspects of New Drug Delivery System. An important avenue of Oral NDDS is its application as “Extended Drug Delivery System” which enables dosing of drug in a sustained or controlled manner so as to provide greater patient acceptance and improved efficacy over conventional therapy. The factors influencing the performance of ER DDS have been reviewed in light of technological and economic feasibility in “ER matrix tablet”. ER product evaluations for drug availability including in vitro measurements, stability requirements and Regulatory considerations have been mentioned followed by the Scale-Up and Post Approval Changes (SUPAC).
Thus, there is a need to design and evaluate controlled release dosage forms on scientific basis in form of tablets. Against this background, it was considered of interest to design and develop solid oral extended release drug delivery system of antihypertensive drug metoprolol tartrate. The objective also included undertaking in vitro evaluation. The objective of the work also kept in mind the possibility of scaling up.

9.6. CHAPTER 5. LITERATURE SURVEY

In order to develop a robust formulation on scientific basis, help was taken of the work done earlier on these as given in the published data. Hydrophilic matrix controlled release systems (along with their advantages and limitations) and the selection of suitable polymer such as HPMC are discussed.

The chapter also deals with the literature reports on the drug molecule employed in this research work. The literature covers the general profiles of these drugs including their description, solubility, therapeutic category, toxicity, storage conditions, handling, precautions etc.

Apart from the above details, literature on pharmacokinetic and pharmacodynamic parameters, their stability, and dosage forms available in the market or mentioned in the literature are also reported. Analytical methods like spectroscopic, chromatographic that can be used for evaluation and characterization of drugs in solid state as well as in solution form have been described with suitable references.
9.7. CHAPTER 6. INTRODUCTION TO EXPERIMENTAL WORK

This chapter reports different methods published in the literature that form basis for the experimental work done in this study. The chapter includes method for calculation of the dose using different models; describes possible oral extended release systems, importance of preformulation studies, including physical, chemical and spectral methods for their identification.

The chapter also describes in details the Extended Release Tablet Dosage Form with emphasis on technique for manufacturing, steps involved, and different types of processes yielding product. Optimization of the process, evaluation of the dosage form, with emphasis on in vitro dissolution methods followed by scale up considerations are also discussed.

9.8. CHAPTER 7. MATERIALS AND METHOD

From here on, the experimental work and discussion goes on. Preformulation Studies were undertaken for physicocemical characterization of the drug with polymer and excipients to establish compatibility before taking up formulation studies.

The method of validation of analytical methods used and the official and unofficial method of evaluation used in the study of developed ER tablet of metoprolol are also dealt. The mathematical treatments used for the obtained data to arrive and meaningful conclusions are also described.

9.9. CHAPTER 8. RESULTS AND DISCUSSION

9.9.1. Physicochemical Characterization of Materials

From the literature provided with the materials and the tests performed; the drug Metoprolol Tartrate (Table 8.1); polymers - HPMC K4M and K100M (Table 7.2);
excipients - Lactose Monohydrate (Section 7.A.3) and Magnesium Stearate (Section 7.A.4) were quality raw material or of official specifications for purity and limit of impurities (Table 7.2 and 8.1); were suitable for use in fabrication of ER DDS of Metoprolol Tartrate.

9.9.2. Drug-Excipient Compatibility Studies

9.9.2.i. Fourier Transform Infra Red Spectroscopy

The overlay curves of pure drug metoprolol tartrate (curve A) with polymer and excipients exhibiting characteristic identical peak absorption at same wave number (fig. 8.12, 8.13, 8.14 and 8.15) indicate the absence of chemical interactions between the active drug and the selected polymer, excipients.

9.9.2.ii. Chromatography

The similar identical $R_{f}$ values for the pure drug metoprolol tartrate (spot A), polymer (spot B & F), and other excipients (spot C, D, G and H) again confirm the absence of chemical interactions between the active drug and the selected polymer, excipients (fig.8.16 and 8.17).


The instrumetl method and validation tests in terms of accuracy (Table 8.7), precision of assay (Table 8.8), ruggedness for in vitro dissolution (Table 8.9), specificity (Table 8.10), limit of detection and quantification (fig. 8.20), linearity and range (Table 8.5 and Fig. 8.18), absorption stability (fig. 8.19) at 275 nm (absorption $\lambda_{max}$) in pH 6.8 phosphate buffer and indicative that the spectrophotometric method of selected drug metoprolol tartrate is suitable for method of drug analysis/estimation.
9.9.4. Standard Calibration Curve and Spectral Absorption Stability for Metoprolol Tartrate

The Beer's Law was found to obey between ~ 0-280 µgm/mL (Fig. 8.18) and the drug was stable for 3 days/more (fig. 8.19) for UV-spectral analysis in pH 6.8 phosphate buffer.

9.9.5. Dosage Design and Preformulation Studies

The powder and granule properties of drug and polymer were characterized for it has tremendous influence on tablet and tabelling properties. The physico-chemical properties of the drug were studied (Table 8.1). Though the drug has got inherent properties for tabletting, the flow properties were poor (angle of repose 45°23'). The particle size distribution of control release polymers was determined by sieve analysis (fig. 8.1 and 8.2), 90% of the polymer size was below 150 µm.

9.9.6. Method of fabrication, formulation variables in the design of ER DDS of Metoprolol Tartrate

Based on the results of performance studies, the formulation work was initiated and is covered in sections 7.B.4 with the justification. Wet granulation technique followed by direct compression method was used (fig. 7.1). Initially, 11 formulations were prepared at fixed concentration of drug and varying concentrations of controlled release polymer and its blend (Table 7.3 and fig. 7.1).

9.9.7. Evaluation of Formulations and Selection of Batch for Scale up

The fabricated matrix systems were evaluated for its organanoleptic properties (appearance, color, texture etc.), hardness, friability, weight variation, content uniformity, disintegration (Table 8.11 and 8.12); and also in vitro dissolution for 24 hours (Table 8.13; Fig. 8.20, 8.21 and 8.22) with Reference Listed Drug Seloken XL 50 of AstraZenca.
9.9.7. Pilot Batch and Product Optimization

The justification for selection of pilot batch from the various batches is discussed in Section 7.B.4.2. The Master Formula is given in Table Section 7.B.6. The granules and tablets were evaluated for the (i) moisture on compressibility (Table 8.14); (ii) temperature (Table 8.15); (iii) temperature and moisture (Table 8.17); (iv) effect of lubrication (Table 8.18); (v) significant granule and tablet properties like Tapped density, bulk density, Carr's Index, Hausner Ratio, Angle of Repose, Uniformity of drug distribution etc (Table 8.18 and 8.19).

9.9.8. Accelerated Stability Studies

Short term (6 months) accelerated stability study was carried out in PVC-PVDC blister as per the ICH guidelines for Zone IV. The tablets were found to be stable (Table 8.20, 8.21 and fig. 8.25). The tablet showed uniformity in content and dissolution. No change in physical, chemical or dissolution characteristics in tablets on Accelerated were observed for a period of 6 months.

9.9.10. Static Swelling Studies

The static swelling studies were performed at room temperature. Anisotropic swelling of the matrix is observed (Table 8.22; fig. 8.26; 27, 28).

9.9.11. In Vitro Release and Mathematical Modelling of Pilot Batch with RLD Seloken-XL

The in vitro release data with the mathematically modeling data for pilot batch D, optimizing batch and RLD is given in Table 8.23, 8.24 and 8.25. Mathematical modeling of scaled up formulation revealed that the release of the drug from the tablet followed 1st Order Fickian kinetics as computed by Korsmeyer-Peppas equation and Higuchi's equation. The release mechanism is by the combination mechanism of swelling and diffusion.
9.9.12. **In vitro Dissolution Profile Comparison**

The mathematical fit factor has been calculated in this work using the dissolution data obtained for the Pilot Batch and the RLD Seloken XL 50. The value of $f_2$ found was 63.8966 indicated thereby that the profiles are equivalent.

Based on the $f_2$ factor, it clearly indicated that the preparation developed in the laboratory was similar to the reference ER preparation.

9.10. **CONCLUSIONS**

The study commenced with the objective to

1. Understand PharmTech Industry;
2. Undertake a survey in hypertensive patients to study their attitude for one's own aging symptoms; and non-compliance to pharmacological and non-pharmacological means of controlling the high blood pressure;
3. Evaluate 50 IR generic forms of marketed product and compare the cost factor incurred in the drug therapy; and
4. Develop and evaluate extended release formulations of metoprolol tartrate using hydrophilic polymers, optimize the formulation and process variable, scale up desired batch and study tablet and tabletting properties with respect to ANDA and SUPAC.

The work reported here clearly indicates the stepwise approach of the set objective. The results indicated the objective of the work undertaken has been completely achieved.