Chapter 3

RESEARCH ENVISAGED
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3. RESEARCH ENVISAGED

3.1 Background

Controlled release oral drug delivery systems have been shown to more advantages over conventional systems\textsuperscript{142-145}. These include increased patient compliance, selective pharmacological action; reduced side effect and reduced dosing frequency. These systems may therefore have a significantly beneficial outcome in therapeutic efficacy. Controlled release offers prolonged delivery of drugs and maintenance of plasma levels within a therapeutic range\textsuperscript{146,147}. Furthermore, by pairing drug administration rate with drug elimination rate, steady state plasma levels can be maintained\textsuperscript{148}. Currently most drug delivery systems exhibit first order drug release kinetics where the plasma level of the drug is extremely high after administration and then decreases exponentially. This poses disadvantages such as minimal therapeutic efficacy due to reduced drug levels or drug toxicity which can occur at high concentrations\textsuperscript{149}. This type of drug release does not allow for appropriate plasma drug level balance. Drug delivery systems should ideally exhibit zero-order drug release kinetics which allows for a constant quantity of drug to be released over an extended period of time, resulting in uniform and sustained drug delivery\textsuperscript{150,151}. Zero-order is a desired drug release kinetic in antibiotic delivery, the treatment of hypertension, pain management, antidepressant delivery and numerous other conditions that require constant plasma drug levels\textsuperscript{152}. Thus, various studies
have been undertaken attempting to develop systems that are easily able to provide zero-order or near zero-order drug release\textsuperscript{153}.

### 3.2 Suitability of a drug

- Among $\beta_1$ receptor blocker Metoprolol succinate is a cardio selective $\beta$ blocker used in the treatment of hypertension, angina pectoris and heart failure.

- Amount of drug available Metoprolol succinate in oral doses is up to 50% so we can increases the bioavailability of drug through controlled release matrix tablets and matrix transdermal drug delivery system.

- Plasma level is 3-7 h and it is having first pass effect but in case of matrix tablet (or) matrix transdermal patches, the first-pass metabolism of drug has been avoided.

- To meet the need for effective and well tolerated $\beta_1$ blockage, an controlled release formulation of Metoprolol succinate is beneficial to meet the objectives of providing once daily dosing that maintains therapeutic plasma concentration.

- By entrapment of drug in the form of matrix tablet (or) transdermal film, the dose could be minimized and reduce the frequency of administration.

- To improve the patient compliance.
Matrix systems are widely used in oral controlled drug delivery because of their flexibility in obtaining a desirable drug release profile, cost effectiveness and broad regulatory acceptance.

By considering the above points the Metoprolol succinate might be a right and suitable candidate for the design of matrix tablet and matrix transdermal patches.

**3.3 Aim and objective of work**

The aim of present investigation is the development and evaluation of controlled drug delivery system for Selective $\beta_1$ receptor blocker of Metoprolol succinate with the following objectives

1. To prepare the controlled release matrix tablets and matrix type transdermal patches with varying proportions of polymers.
2. To study the drug and polymer interaction.
3. To produce better bioavailability.
4. To minimize the dose.
5. To avoid first pass metabolism of the drug within the gastrointestinal tract.
6. A prolong period of time observed in within the GIT and skin.
7. Improve the patient compliance.

**3.4 Plan of work**

Conventional oral drug delivery systems are slowly departure away in the market due to disadvantages. It produce fluctuation of
drug plasma level that either exist at safe therapeutic level or quickly falls below the minimum effective level which is due to half life, frequency of administration and release rate. It is standard that many patients can benefit from drugs intended for chronic administration by maintaining the plasma level with in a safe effective range. Controlled drug delivery systems are highly recognized today for their benefits as from the dosage form drug must be released at predetermined rate in GI fluids, maintain enough residence time and be absorbed at a rate that will replace the amount of drug being metabolized and excreted. These are used in the treatment of chronic rather than the acute condition and they posses good margin of safety. The work entitled “Formulation and evaluation of different controlled release drug delivery system for selected cardio vascular drug” was planned in an aim to achieve the objectives. The experimental work composed of preformulation studies, formulation and evaluation of controlled release matrix tablets and matrix transdermal drug delivery system of Metoprolol succinate.

**Phase I Preformulation studies**

- Selection and collection of raw materials
- Drug-polymer compatibility studies by Physical observation
- Drug-polymer interaction studies by FTIR
- Drug-polymer interaction studies by DSC
- UV spectroscopic method development
- Construction of calibration curve
Phase II Formulation and evaluation of controlled release matrix tablets

- Optimization of formulations of matrix tablet by $2^3$ factorial design.

- Formulation of controlled release matrix tablets of Metoprolol succinate by wet granulation method

- Evaluation of micromeritic properties of prepared granules
  - Bulk density
  - Tapped density
  - Angle of repose
  - Compressibility index
  - Hausner’s ratio

- Evaluation of physicochemical characterization of prepared matrix tablets
  - Thickness
  - Weight variation
  - Hardness
  - Friability
  - Drug content

- \textit{In-vitro} drug release and kinetic studies

- \textit{In-vivo} drug release kinetics
• In-vitro In-vivo correlation

• Stability studies and statistical analysis

**Phase III Formulation and evaluation of controlled release matrix transdermal patches of Metoprolol succinate**

• Optimization of formulations of matrix transdermal patches by $2^3$ factorial design.

• Formulation of controlled release matrix transdermal patches of Metoprolol succinate by solvent casting method

• Physiochemical evaluation of matrix transdermal patches of Metoprolol succinate
  
  o Thickness and Weight
  
  o Flatness
  
  o Folding endurance
  
  o Surface pH
  
  o Percentage moisture absorption
  
  o Percentage moisture loss
  
  o Water vapor transmission rate
  
  o Drug content

• Scanning electron microscopy

• Measurement of mechanical strength
• Skin irritation studies through rat skin by Draize scoring method

• *In-vitro* drug permeation and kinetic studies

• *Ex-vivo* skin permeation through rat abdominal and porcine skin

• *In-vivo* drug absorption study using rabbits

• *In-vivo* drug absorption kinetics

• Correlation studies

• Stability studies and statistical analysis