Chapter 3

RESEARCH ENVISAGED
## Chapter 3

RESEARCH ENVISAGED

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Name of the Sub-Title</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1.</td>
<td>Background</td>
<td>54</td>
</tr>
<tr>
<td>3.2.</td>
<td>Suitability of a Drug</td>
<td>57</td>
</tr>
<tr>
<td>3.3.</td>
<td>Aim and Objective of Work</td>
<td>58</td>
</tr>
<tr>
<td>3.4.</td>
<td>Plan of Work</td>
<td>58</td>
</tr>
</tbody>
</table>
3. RESEARCH ENVISAGED

3.1. Background

Anti-hypertensive drugs currently available in clinical use have several shortcomings such as poor absorption due to narrow absorption window and large side effects due to high dose and toxicity. These reasons are more beneficial from compounding into a controlled drug delivery system. Replacing parenteral administration of drugs to oral pharmacotherapy would significantly improve the treatment. It is anticipated that controlled drug delivery systems may enhance this possibility.

Controlled release oral drug delivery systems have shown more advantages over conventional systems\textsuperscript{142-145}. These include drug release at predetermined period and rate, reduced fluctuation in plasma drug concentration, reduced side effect and dosing frequency, increased patient compliance, etc. 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, steady state plasma levels can be maintained\textsuperscript{148} by pairing drug administration rate with drug elimination rate. 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 it decreases exponentially. This possesses 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 allow 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 to develop systems that are easily able to provide zero-order or near zero-order drug release\textsuperscript{153}.

Moreover, it is expected that the controlled delivery systems approach may be used for many potential active agents with a poor delivery of drug in absorption window, whose development has been halted due to the lack of appropriate drug delivery technologies. It was decided to implement the modern technology by utilizing suitable polymer matrices.

Literature survey revealed that the flowing problems have been observed from the previous works done on the controlled drug delivery systems for antihypertensive drugs and they include:

- Fluctuations in drug plasma concentration.
- Selectivity in receptor activation.
- Counter activity of the body.
- Extended time over critical (effective) concentration.
- Adverse activity at the colon.
• Lack of desired properties of polymers used e.g., swellability and diffusivity.

• Not suitable polymers were used to achieve controlled drug release mechanism.

• More difficult methods have been adopted to design the dosage form.

• More number of synthetic polymers and less number of natural polymers were used to develop the drug delivery systems.

• The natural polymers provide many advantages which are not studied well.

These accumulated findings warrant an additional research on controlled drug delivery systems with biocompatible and biodegradable natural polymers, which combine large dimensions with high rigidity to achieve controlled drug release.

It is expected that the extension of applications of swellability, diffusivity, and biocompatible and biodegradable properties may yield a deeper insight into the mechanisms of gastroretentivity. This could lead to a more systemic and intelligent design of CDDS.

It was believed that these problems can be overcome by CDDS, which is interesting and present their own advantages. In the future, it is expected that they will become increasingly important, leading to improved efficiencies of pharmacotherapy.
3.2. Suitability of a Drug

- Bosentan is an oral medication classified as an endothelin receptor antagonist (ERA), which is approved for the treatment of pulmonary arterial hypertension (PAH) Group 1 patients.

- The amount of drug available in plasma is up to 50% so that the bioavailability of the drug can be increased through controlled release matrix tablets, pulsincap, and mini-tablets.

- The half life of the drug is about 5 hours and it is having a first pass effect but in case of the matrix tablet, pulsincap, and mini-tablets, the first-pass metabolism of drug has been minimized.

- By blocking the action of endothelin causing vessels to relax, bosentan decreases the pulmonary blood pressure to the heart and improves its function. This generally results in the ability to be more active. Research studies have verified this improvement.

- Controlled release formulation with bosentan is beneficial to meet the objectives of providing daily dosing that maintains therapeutic plasma concentration.

- By entrapment of drug into controlled release formulations, the dose could be minimized and the frequency of administration could be reduced.

- 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, bosentan might be a right and suitable candidate for the design of matrix tablet, pulsincap, and mini-tablet formulations\textsuperscript{99,154}.

3.3. Aim and Objective of Work

The aim of the present investigation is to design, develop, and characterize the controlled drug delivery system for the treatment of pulmonary arterial hypertension (PAH) with the following objectives.

1. To prepare the controlled release matrix tablets, pulsincap and matrix type mini-tablet formulations with varying proportions of selective polymers.
2. To study the drug and polymer interactions.
3. To enhance the bioavailability.
4. To minimize the dosing frequency.
5. To minimize the first pass metabolism of the drug within the gastrointestinal tract.
6. To release the drug for a prolonged period of time within the GIT.
7. To improve the patient compliance.

3.4. Plan of Work

Conventional oral drug delivery systems are slowly vanishing from the market due to some disadvantages. They produce fluctuation of drug plasma level that either exists at safe therapeutic level or quickly falls below the minimum effective level, which is due to half life, frequency of administration, and release rate. Many patients can benefit from the drugs intended for chronic administration by
maintaining the plasma level within a safe, effective range. Today, controlled drug delivery systems are highly recognized for their benefits. From the dosage form, the drug must be released at a predetermined rate in GI fluids, enough residence time should be maintained, and it should 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 acute conditions and they possess good margin of safety.

The work entitled “DEVELOPMENT AND EVALUATION OF CONTROLLED DRUG DELIVERY SYSTEMS OF ANTIHYPERTENSIVE DRUG” was planned with an aim to achieve the objectives. The experimental work composed of preformulation studies and design and development of novel controlled release formulations such as matrix tablets, pulsincap, and matrix mini-tablets of bosentan and its evaluation.

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 and HPLC analytical methods of development
- Construction of calibration curve of bosentan
Phase II - Design and Development of Novel Controlled Release Formulations and its Evaluations

- QBD based optimization of formulations from various approaches such as matrix tablets, pulsincap, and matrix mini-tablets by $2^3$ factorial design using Design Expert software v8.0.7.1, Stat-Ease Inc., Minneapolis, MN, United States of America.

- Formulation of controlled release matrix tablets of bosentan by wet granulation method.

- Formulation of pulsincaps of bosentan filled with pellets and hydrogel plug for controlled release.

- Formulation of matrix mini-tablets by direct compression method further filled into the treated insoluble hard gelatin capsules.

- Evaluation of derived and flow properties of prepared granules using the following parameters:
  - Bulk density
  - Tapped density
  - Angle of repose
  - Compressibility index
  - Hausner’s ratio

- Evaluation of physicochemical characterization of developed formulations using the following parameters:
  - Thickness
  - Weight variation
- Hardness
- Friability
- Drug content
- Equilibrium swelling ratio
- Water uptake studies
- Evaluation of gel fraction
- In-vitro drug release and kinetic studies
- In-vivo drug release kinetics
- In-vitro and in-vivo correlation
- Stability studies and statistical analysis
- Comparison of best formulation with marketed formulation