Chapter 4

PLAN OF WORK
Objective

Diltiazem is a widely used drug for the treatment of various cardiovascular disorders. Due to its short half-life in conventional dosage forms a number of sustained release products have been introduced in the market for once a day administration. *In vitro* dissolution profiles of various sustained release products of leading Indian pharmaceutical companies were carried out by us but all the formulations released 100% drug within 16-18 hours and none of them released the drug up to 24 hours (fig. 4.1). These formulations when given to patients may, therefore, not provide therapeutic plasma concentration over a period of 24 hours, hence they are not suitable for once a day treatment. The present investigation was aimed with an approach to develop an oral osmotic pump of DL that can provide controlled delivery of drug up to 24 hours with prospects of better therapy, improved patient compliance and least side effects.

Plan of Work

The present study has been undertaken on the following lines:

- **Preformulation**
  - To carry out compatibility study of drug with various excipients to find any physical and chemical changes.
  - Selection of osmotic agent and osmopolymers.
  - Selection of polymer to make semipermeable membrane.
  - Selection of granulation solvent
• Selection of solvent for polymer for semipermeable membrane
• Optimization of binder and lubricants quantity.
• Estimation procedures and standard curves for the quantitative estimation of drug in various media (0.1 N HCl, phosphate buffer pH 6.8 and 7.4, purified water) and plasma.
• Optimization of compression and coating parameters.

**In vitro characterization of polymeric membrane with different plasticizers.**
• Preparation of film with cast film method.
• To study mechanical properties of polymer film.
• To study water permeability of polymer film.
• To study effect of plasticizer and their concentration on glass transition temperature.

**To determine in vitro dissolution profile of various sustained release products available in Indian market.**

**Use of Response Surface method to**
• Generate a equation to predict release profile from the osmotic pump.
• Determine interaction of various variables on dissolution.
- Optimize quantity of osmotic agent, osmopolymers and coating thickness.

**Evaluation of osmotic pump**

- Appearance
- Hardness, thickness, weight variation
- Friability
- Film thickness, pore diameter
- Surface area and volume
- Water content
- Assay

**In vitro characterization of osmotic pump to study effect of**

- pH of media on dissolution
- Stirring conditions on dissolution
- Pore size on dissolution
- Number of pores on dissolution
- Push compartment on dissolution
- Type of membrane composition on dissolution
- Membrane thickness on dissolution.
- Type of orifice drilling machine
- With and without immediate release dose
- Scale up the batch size and study its effect on dissolution
To carry out stability study of the final formulation in suitable packing at

- 25°C, 60% RH
- 60°C
- 40°C, 75% RH

To study bioavailability (in human) and in vivo - in vitro release characteristic of drug from osmotic pumps.

FIGURE 4.1: Dissolution profile of various Indian sustained release formulations of diltiazem HCl (Media 0.1 N HCl).