3. NEED AND OBJECTIVES OF WORK

3.1 Need of Work

Aqueous solubility is one of the key determinants in development of new chemical entities as successful drugs. Various formulation techniques are applied to compensate for their insolubility and consequent slow dissolution rate. These include formulation of the amorphous solid form, nanoparticles, microemulsions, solid dispersion, melt extrusion, salt formation and formation of water soluble complexes. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the parameters to achieve the desired concentration of drug in systemic circulation for pharmacological response to be shown.

Currently only 8% of new drug candidates have both high solubility and permeability. It has been estimated that roughly 40% of all investigational compounds fail development because of poor bioavailability that is often associated with aqueous insolubility.

Simvastatin is a cholesterol-lowering agent, widely used to treat hypercholesteremia and dyslipidemia. It is practically insoluble in water, poorly absorbed from the GIT. It has half life of 2 h, bioavailability of 5% and protein binding 98%.

Lovastatin is a cholesterol reducing agent, practically insoluble in water and its the extensive first-pass effect results in low systemic bioavailability, leaving only a small amount (<5%) in the systemic circulation. Therefore, it is very important to devise effective methods to enhance the solubility and dissolution rate of drug, consequently increasing its bioavailability.

Elevation of the total cholesterol in plasma is considered to be a prime risk factor for coronary heart disease. Statins are highly efficacious in lowering cholesterol in plasma. So, there was need to prepare and evaluate nanoparticles of statin drugs, which improve solubility, dissolution rate, and bioavailability.

In the recent years, nanoparticle technology has emerged as a strategy to tackle such formulation problems associated with poorly water-soluble drugs. The reduction of drug particle to the nano-scale increases dissolution velocity and saturation solubility, which leads to improved in vivo drug performance. One such approach in this direction is the use of nanoparticles drug carrier that can improve the solubility and ultimately bioavailability with optimum drug release profile.

The objective of the present study was to formulate simvastatin and lovastatin nanoparticles by precipitation- solvent displacement and inotropic gelation method for oral drug delivery, and check the potential of nanoparticles to enhance bioavailability of lipophilic drugs.
The study was to entrap hydrophobic molecule (lovastatin) into hydrophilic nanoparticles formed by the process of ionotropic gelation based on the interaction between the negative groups of the sodium tripolyphosphate (STPP) and the positively charged amino groups of chitosan. Hydrophobic polymer like polylactic co-glycolic acid (PLGA) and hydrophilic polymer like chitosan can be used in preparation of nanoparticles. Stabilizers like pluronic F68 (surfactant) and sodium tripolyphosphate (STPP) as cross linking agent can be used. Bioavailability of simvastatin and lovastatin loaded nanoparticles can be compared with marketed formulation and suspension of simvastatin and lovastatin to conclude the findings of the work.

The present work has been designed to provide a stable drug delivery system with improved therapeutic index for simvastatin and lovastatin in the form of nanoparticles.

### 3.2 Objectives of the work

The important objective of proposed research work are-

1. To prepare simvastatin loaded nanoparticles using Precipitation-solvent displacement method.
2. To prepare lovastatin loaded nanoparticles using and Inotropic gelation method.
   a) To prepare batches of drugs loaded nanoparticles by $3^2$ factorial design.
   b) To evaluate suspension of simvastatin and lovastatin-loaded nanoparticles for entrapment efficiency, particle size, zeta potential and to carry out intensive study of results obtained in order to determine a suitable batch as an optimized batch.
   c) To investigate the effects of freeze-drying on particle size and release characteristics of simvastatin and lovastatin loaded nanoparticles.
   d) To evaluate formulations by Fourier Transform infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC), Powder X-Ray Diffraction Studies (PXRD), Scanning electron microscopy (SEM), Transmission electron microscopy (TEM) and In vitro drug release study.
   e) To evaluate optimized formulation antihyperlipidemic activity on albino rats and estimation of pharmacokinetic parameters using albino rabbits.
   g) Accelerated stability studies to determine product performance, in vitro efficacy and stability.