Today more than 70% of newly discovered oral drugs (independent from the therapeutic class) are poorly soluble with low bioavailability which may result in a serious challenge to the development of new compounds. There are several drug formulations strategies available to further improve the solubility and/or dissolution rate, i.e., solid dispersion technique, self-emulsifying systems or complex formation. These strategies have been successfully used in the past but today nanotechnology has produced a massive impact to meet the needs. Various factors particularly economic, social, public health and environmental benefits have together made nanotechnology as drug delivery systems a very popular. Poorly soluble oral drugs often encounter low bioavailability and erratic absorption patterns in the clinical setting. Due to the rising number of compounds having solubility issues, finding ways to enhance the solubility of oral drugs is one of the major concerns in the pharmaceutical industry today. Polymeric nanoparticles, which form upon self-assembly of macromolecules, act as solubilizing agents for delivery of poorly soluble oral drugs.

1.2 Polymeric Drug Delivery

Polymeric nanoparticles have been extensively investigated over the last two decades after the first report was published in 1976 (Birrenbach et al., 1976). These polymeric nanoparticles as drug carrier or the carrier of tracer molecules have been presented as solid nanospheres where the active substances have been incorporated either inside or adsorbed on their surfaces or both. They are also presented as nano-capsules where the active substances have either been incorporated within the core or loaded on the surface by chemical bonding or physical adsorption (Allemann et al., 1993).

The polymeric nanoparticles (PNPs) have been prepared from biocompatible and biodegradable polymers in size between 10-1000nm where the drug is dissolved, entrapped, encapsulated or attached to a matrix material (Soppimath et al., 2001; Mohanraj et al., 2006).

Polymer based nanoparticles effectively carry drugs, protein and DNA to the target cells and organs. Their nanometer size promotes effective permeation through cell membranes and also responsible for stability in the blood stream (Peer et al., 2007). Non-toxic, nano-sized polymers

in controlled drug delivery are nevertheless thought to be playing important role, and it has been hypothesized that while the drug should be delivered at rates that maintains its optimum therapeutic activity at the active sites, concurrently the side effects should be brought down to the lowest level (Illum et al., 1987).

Delivery of the drugs especially poorly soluble drugs through the polymeric nanoparticles is considered to assist in reducing the adverse reactions and side effects. Polymeric nanoparticles are chosen because of several characteristics that have been identified and summarized as given below:

a) The polymers should be compatible with the human system in terms of adaptability (non-toxicity and non-antigenicity) and should also be biodegradable as well as biocompatible.
b) The particles should preserve and protect the drugs and should not release them till they reach the site of action.
c) The nanoparticles should not interact or should not have any harmful effects on the body cells or the tissues.
d) The particles should be able to traverse the intervening membranes.
e) The particles should recognize the sites of action and should get bound or associated with the site of action.
f) The drugs should be released at rates so as to achieve the desired therapeutic effects on a continuous basis.
g) After the release of the drugs, the nanoparticles should be degraded or eliminated from the human system (Davis S et al., 1985; Miyazaki et al., 1986; Verdun C et al., 1986; Jalil et al., 1990; Ohya O et al., 1991).

1.3 Polymeric Nanoparticles for the Delivery of Poorly Soluble Drugs

In order to entrap water-insoluble bioactive substances investigation and advancements have been made using hydrophilic nanoparticles of polymeric nanoparticles during the recent time (Kwon et al., 1995; Kwon et al., 1996; Riess et al., 1985). The poorly bioavailable drugs such as Amphotericin B, Ketoconazole, Ciprofloxacin, Vancomycin and Chloramphenicol have been physically entrapped in the core of polymeric nanoparticles composites. Polymers have been playing an integral role as carrier in formulating an efficient drug delivery system by their

stability, drug loading capacity and tunable properties. Polymer based drug delivery systems can improve the pharmacokinetic profile of a drug, improve their therapeutic index, decrease their side effects and hence increase the efficiency of the whole system. Biodegradable as well as biocompatible polymers are best suggested for this application because of the need of appropriate release of the drug as well as easy removal of the carrier after drug administration (Thanou et al., 2001).

In particular, the potential of polymeric nanoparticles for the delivery of poorly water-soluble drugs, especially in the area of oral delivery is discussed. Key considerations in utilizing chitosan nanoparticles advantages and chitosan nanoparticles encapsulated with poorly soluble oral drugs preparation, characterization, antimicrobial activity *in-vitro* release study and kinetic modeling of drug release were highlighted. Polymeric nanoparticles (chitosan nanoparticle) have gained much attraction for the drug delivery systems in the last few decades owing to their ability for the delivery of the drugs in a sustained manner at the site of action (McCarron et al., 2008). Biodegradable polymeric nanoparticles were lot more useful for developing controlled and sustained release together with patient compliance (Goyal et al., 2010). Also biodegradable nanoparticles exhibit constant rate of degradation, which can be beneficial in terms of sustained drug release approach (Gunatillake et al., 2003). Chitosan is chosen as a polymer because it is selected widely in preparation of various drugs delivery systems (Lam et al., 2000; Cohen et al., 1991; Whittlesey et al., 2004). These biodegradable nanoforms such as chitosan nanoparticles for the sustained drug delivery can reduce the serious systemic side effects caused after the drug administration (Mu et al., 2003; Okada et al., 1995). Particle size, surface morphology, size distribution, drug content have a major effect on the sustained drug release from the hydrophilic polymeric chitosan nanoparticles (Gabor et al., 1999). Objective of the present study was mainly designed to overcome some major challenges in the development of carrier molecule for the delivery of poorly water soluble oral drugs. Chitosan is one of the suitable components due to its various features which make it perfect for the carrier design and also it is believed to be one of the most promising materials for the purpose of drug delivery. Based on the information from different published literatures available, we designed a nanocarrier combining unique properties of low molecular weight chitosan with TPP, a polyanion (Calvo et al., 1997). Chitosan possess the main characteristics of biocompatibility and biodegradability which are essential requirement for the safer and effective delivery of poorly soluble drugs into cells.

Nanoparticles resulting from this polymeric combination provide desirable attributes for poorly soluble drugs applications in terms of size, charge and *in-vitro* release study. In this research, we have prepared four types of formulations of chitosan nanoparticles and single formulation of thiolated chitosan nanoparticles loaded with poorly soluble oral drugs such as Amphotericin B, Ketoconazole, Ciprofloxacin, Vancomycin and Chloramphenicol. These nanoparticles loaded with drug further optimized and characterized on the basis of SEM study, FTIR plots, XRD spectra, Zeta-potential value, drug entrapment efficiency, practical yield, cumulative *in-vitro* release profile, antimicrobial activity and kinetic modeling (Zero-order, First-order, Higuchi, Korsmeyer-Peppas and Hixon models) of drug release from nanoparticle formulation.

Objectives of this research

- Selection of polymeric matrix material.
- Preparation of polymeric nanoparticles (chitosan and thiolated chitosan nanoparticles).
- Optimization of parameters for the preparation of polymeric nanoparticles to achieve desired size range and maximum drug entrapment efficiency.
- Loading of poorly soluble oral drug (Amphotericin B, Ketoconazole, Ciprofloxacin, Vancomycin, Chloramphenicol) actively into the polymeric nanoparticle. These oral drugs are chosen because of their low bioavailability.
- Characterization of drug loaded polymeric nanoparticles.
- Scanning electron microscopy of drug loaded polymeric nanoparticles.
- Zeta-potential for the stability of drug loaded polymeric nanoparticles.
- Fourier transform infra red spectroscopy of drug loaded polymeric nanoparticles.
- X-ray diffraction study of drug loaded polymeric nanoparticles.
- Drug entrapment efficiency calculation.
- Percentage yield calculation.
- Antimicrobial activity.
- Comparative study of cumulative *in-vitro* drug release from chitosan, thiolated chitosan nano-formulations and free drug itself.
- Statistical analysis of data.
- Kinetic modeling of drug release from chitosan nanoparticle formulation CS1 and kinetic modeling of free drug.