11. SUMMARY AND CONCLUSION

Most conventional oral dosage forms, such as tablets and capsules are formulated to release the active drug immediately after oral administration to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. This may lead to fall in plasma drug concentrations below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity.

Controlled drug delivery systems can be effective in producing sustained action at predetermined rate, localized targeted action and minimized side effects with improved pharmacological effect. This may lead to overcome the patient compliance problems and also with cost effective.

Nanoparticles are drug delivery system, which can also be operated as controlled drug delivery. These systems have some peculiar properties such as increased surface area, specific targeting, optical properties and less toxicity when compared to other systems. Nano systems provide an efficient way of drug delivery particularly for chronic therapy management.

Lansoprazole is a drug commonly used in the management of peptic ulcer in various conditions such as acid-related disorders of the upper GIT, gastro esophageal reflux disease, benign gastric ulcer and duodenal ulcer. This drug, on regular usage, is reported to cause adverse effects including abdominal pain, diarrhoea, dizziness, skin rashes, angioedema, thrombocytopenia, impotence etc.

Further the gastro-intestinal tract is exposed to different pH environment, which the lansoprazole may be wasted. Hence targeting of the drug to peptic ulcer should also be considered in designing a suitable drug delivery system. Its short half-life (1 – 1.5hrs), which demands frequent administration and severe side effects demands the
development of a controlled release formulation. Thus the overall aim and objective of the present work was to:

- Improve the overall therapeutic efficacy of lansoprazole by controlled release using nanoparticles drug delivery
- Targeting the drug to peptic ulcer cells.
- Minimize the adverse effects
- Reduce the overall dose and dosing frequency of lansoprazole
- Achieve improved patient compliance

To achieve the goals oral controlled drug delivery system nanoparticles of lansoprazole was developed, optimized and evaluated both *in vitro* and *in vivo*

The preformulation studies were performed for the lansoprazole and excipients. The melting point, loss on drying, angle of repose, bulk density, tap density, Hausner’s ratio, compressibility index for the drug were calculated. The flow property studies indicated that the lansoprazole has poor flow properties.

Compatibility studies of IR and DSC were performed and these reports suggested no chemical interaction between lansoprazole and the polymers/excipients used for the development of various formulations.

Before performing the formulation, initially, insoluble body of the capsule is prepared by producing reaction between formaldehyde and potassium permanganate on gelatin. This step is to protect the drug from degradation for first 2 hr.

Lansoprazole loaded chitosan nanoparticles (CNP1 to CNP10) and PLGA nanoparticles (PNP1 to PNP10) were prepared by ionotropic gelation and interfacial deposition method respectively. The product and process parameters were optimized. The prepared NPs were characterized by study of morphological characters,
determination of particle size analysis, zeta potential, drug content, entrapment efficiency, *in vitro* release and stability studies. The prepared nanoparticles were visually observed. The particles obtained were of smooth and free flowing. No visible impurity was seen in both chitosan and PLGA nanoparticles.

The drug content for the lansoprazole loaded chitosan nanoparticles varied from 69.5±7.2% to 87.9±1.2%. But contrast to this result lansoprazole loaded PLGA nanoparticles, the drug content varied from 86.3±1.6% to 90.9±0.6%. This result indicated that there was no drug loss by manufacturing process or by excipients used in the formulation.

The entrapment efficiencies were found to be minimum and maximum of 39.3±2.6% and 85.6±1.2%, 69.3±1.2% and 95.6±0.3% for chitosan and PLGA nanoparticles respectively. The optimum entrapment efficiency was found to be 85.3±0.8% and 95.5±0.6% for chitosan and PLGA nanoparticles respectively. From drug content and entrapment efficiency results chitosan nanoparticles CNP5 and PLGA nanoparticles PNP7 were considered as optimum trials.

The particle size of chitosan nanoparticles varied from 360±12nm to 814±62nm. The mean particle size of chitosan nanoparticles was reduced from CNP1 (620±42nm) to CNP5 (360±12nm) with increase in polymer concentration. But the particle size was increased from CNP5 (360±12nm) to CNP10 (814±62nm) due to increase in polymer concentration. The particle size of PLGA nanoparticles varied from 262±23nm to 710±50nm. In this nanoparticle the mean particle size was reduced from PNP1 (620±50nm) to PNP7 (262±23nm). This may be due to the same reason occurred in chitosan nanoparticle, which is due to avoidance of aggregation of drug particles.

The zeta potential values of chitosan nanoparticles were in positive and increased from 11.2±1.2mV to 18.7±0.4mV. The CNP5 trial held a value of 18.3±0.2mV. The
zeta potential values of PLGA nanoparticles were in negative and increased from -9.2±1.2mV to -32.8±1.8mV. The negative value was due to the nature of PLGA. The results indicated that PLGA nanoparticles were possessing good stability.

From the *in-vitro* release studies of lansoprazole loaded with chitosan nanoparticles (CNP1 – CNP10) and PLGA nanoparticles (PNP1 – PNP10), it was observed that with all formulation, there was absolutely no drug release for initial 2 hours. More concentration of polymer (CNP6 to CNP10 and PNP8 to PNP10) formed slow release of drug for more than 24 hr. Less concentration of polymer (CNP1 to CNP4 and PNP1 to PNP6) formed quick release of drug within short period. Lansoprazole nanoparticles prepared with 0.5% chitosan (CNP5) and 100mg of PLGA (PNP7) showed controlled and sustained drug release for a period of 24 hr. Based on the *in - vitro* drug release study results of Lansoprazole-Chitosan nanoparticles and Lansoprazole-PLGA nanoparticles, the formulation prepared with PLGA have shown desirable drug release rates than the formulation prepared with chitosan.

The optimized chitosan nanoparticles and PLGA nanoparticles were compared to identify the better formulation. The drug content, entrapment efficiency, particle size and zeta potential values for CNP5 and PNP7 were found to be 86.3±0.6%, 85.3±0.8%, 360 ±12nm, 18.3±0.2mV and 90.9±0.6%, 95.5±0.6%, 262±23nm, -30.1±1.2mV respectively. The surface morphology (TEM) of the chitosan nanoparticles were found to be spherical with uneven surface. But the PLGA nanoparticles were found to be spherical with smooth surface. The in vitro release of drug was amazingly same for CNP5 and PNP7. Both formulations followed zero order release indicated the controlled release.

From the results, the formulation PNP7 was considered has optimum than CNP5 and preceded for further *in vivo* studies and stability studies.
The animal studies indicated that the formulation PNP7 was considered more effective than the normal form.

The optimized formulation (PNP7) was subjected to stability studies by storing the samples at three different temperature conditions, i.e 2-8, 25 and 40°C. None of the NP formulations indicated any symptoms of agglomeration or colour change during the period of assessment. Samples were withdrawn at predetermined time intervals of 1, 2, 3 and 6 months and then evaluated for the particle size and drug content. The formulation PNP7 stored at 2-8°C retained the particle size (262nm) with minor variation until 6 months.

The formulations stored at 25°C exhibited a negligible increase in particle size with a minor decrement in the drug content. A considerable increase in particle size was recorded with parallel drug degradation within the period of 6 months. The results showed that there were no considerable changes in the parameters studied, however minor changes observed at elevated temperature conditions. This suggests that the formulations were stable under normal conditions, the ideal storage of the nanoparticle formulation at temperatures is less than 25°C.