Chapter 6

SUMMARY AND CONCLUSION

6.1 Summary

Many peroral sustained DDS are designed to extend drug release. Mainly the API should be absorbed all through the GIT. Usually, the availability of APIs from peroral DDS is prohibited by numerous physiological problems, like incapability to hold back and restrict the drug delivery systems inside preferred area of the GI Tract with high unpredictable character of stomach emptying. Maintenance of oral drug devices in proximal GI Tract increases time of contact of drug with GI wall, thus increased bioavailability, and hence therapy effectiveness, decreased dosing frequency, and thus decreased dose size. So, extended release DDS possessing gastric retention properties may be potentially useful.

In present study three drugs Ondansetron HCl, Ketoprofen and Glipizide were selected for design of various floating drug delivery systems. All three candidates were required to be designed as floating drug delivery system for sustained action of them. For Ondansetron HCl Floating matrix tablet was prepared using natural gums to retain it in stomach for longer time, from where its absorption is better. For Ketoprofen floating drug delivery system were designed, since it is absorbed better from upper part of duodenum and microspheres were prepared to minimize its gastric irritation by reducing the mucosal contact. For Glipizide floating bilayer tablets were developed, since absorption of Glipizide is unpredictable in diabetes patient owing to weakened gastric-mobility and stomach emptying. So the efficacy of the drug was improved.

Ondansetron Hydrochloride is a seratonin 5-HT3 receptor type blocking agent meant for prevention of vomiting and nausea related with preliminary and repeated course of emetogenic cancer-chemotherapy, also in high doses cisplastin.

Various formulation batches were developed for Ondansetron Hydrochloride floating tablet by $3^2$ full factorial design using Xanthan gum and Karaya gum.
Preformulation study of drug and polymers were done by performing IR. Evaluation of powder mixture was done for physical parameters.

Ondansetron Hydrochloride floating tablet batches were formulated and analyzed for friability, hardness, uniformity of content, thickness and weight, floating lag-time, buoyancy duration, dissolution study and accelerated stability study were performed. Optimized formulation was subjected to dissolution study for 12 hrs. Effects of combination of two gums on drug release rate were studied.

Tablets containing Xanthan gum (27.27%, w/w), Gum Karaya (21.81%, w/w), NaHCO3 (18.18%, w/w) and tartaric acid (9.09%) (Formula F4) showed acceptable result in consideration with total floating duration, floating lag-time, swellability, and controlled release rate of drug. Drug release profiles on model fitting of optimized formulation F4 followed Kosymer- Peppas as best-fit model that indicated the release of drug was Anomalous-transport or Non-Fickian through the pores. Stability studies shown that the temperature and moisture doesn’t have much effect on the floating lag time, hardness, drug content and release of drug from floating tablets.

Extended release microspheres of Ketoprofen were produced by ionotropic-gelation method. Various batches were developed by applying 3² full factorial design. Prepared microsphere composed of single gas generating agent and different polymer of different solubility profile such as sterculia and sodium alginate in different ratio. The formulations of microspheres were characterized for micromeritic studies like particle-size, angle of repose, bulk densities, tapped densities, hausners ratio and Carrs index. Moreover they also analyzed for % yield, entrapment of drug and in vitro drug release pattern. Drug: polymer compatibility study by FTIR spectroscopy.

All batches of microspheres studied shown good floating behavior. However, based on drug entrapment, % yield and release pattern study of the formulations, it was observed that the formulation having 75 mg of Ketoprofen and 150 mg sodium bicarbonate with 150mg of sterculia gum and 200mg sodium alginate i.e. batch F4. This batch released 94.08% drug for a period of 12 hrs. also shown good entrapment efficiency of drug and % yield. Since it met the all requirement, selected as the optimized batch and further studied for stability-studies, Scanning Electron Microscopy (SEM) and release kinetics.
FTIR study revealed no interaction in drug and polymer. SEM study confirmed spherical shape and smooth surface of microspheres. Accelerated stability study also showed that formulations were stable for a month at 40 ± 2°C/75 ± 5% RH.

Sustained release bilayer floating tablets of glipizide were developed by applying $2^{3}$ factorial design. Firstly sustained release layer of glipizide were formulated and optimized using HPMC K4M, HPMC K15M and Xanthan gum, then floating layer was optimized using HPMC K100M, Sodium bicarbonate and starch 1500. The manufactured formulations of sustained release layer characterized for drug content, hardness, thickness, in-vitro drug release etc. Bilayer floating tablet was compressed in 8mm die and evaluated for hardness, drug content, thickness, in vitro release of drug, floating time, floating lag time, drug-polymer compatibility study etc.

Among all sustained release layer formulations studied it was observed that, Glipizide release pattern of the matrices was mainly reliant on the polymers swelling, diffusion of drug and erosion of matrix. Formulation A2 was able to retard drug for 12hrs, releasing 98.22% drug in 12hrs. Formulation A6 was able to retard drug for 12hrs, releasing 96.39% drug in 12hrs. Polymer to drug ratio 2:1 shown better retardation due to higher concentration of polymers, while polymer to drug ratio 1:1 was unable to retard the release for 12hrs. When HPMC-K15 M and HPMC-K4 M used in ratios of 9:1 with xanthan gum, they shown more retardation and less than 75% drug released in 12hrs, but when these polymers used in ratio 1:1 with xanthan gum shown better control over release pattern of the drug.

Sustained release layer formulations A2 and A6 were optimized and used for preparation of bilayer tablets. Optimized floating-layer containing HPMC-K 100M (46mg), Sodium bicarbonate (45mg) and starch1500 (49mg). These bilayer tablets shown satisfactory drug release pattern, floating lag period floating time, and followed Higuchi release kinetic, indicative of drug release from the formulation was by diffusion through the intragranular opening formed by porous matrices. This shows that the release of drug was controlled by Fickien diffusions.
6.2 Conclusion:

Ondansetron HCl floating matrix tablet was found to be promising for sustained-release of the drug. Viscosity and concentrations of gums had shown directly proportional relation with swelling properties of tablet. As concentration and viscosity of gums increased, release rate of drug was retarded. Since the concentrations of Xanthan gum increases, percent release rate of drug decreases. So it can be said that Xanthan gum can act as drug release retardant.

From this study it can be concluded that swelling-behaviour of the microsphere was pretentious by the process parameter like concentrations of the gum-sterculia, sodium-alginate and crosslinkers. As well buoyancy of the microspheres was able to retain device in the stomach for extended period and could enhance the bio-availability and therapeutical efficiency of the Ketoprofen. Thus the prepared Ketoprofen sustained release microspheres can be utilized as a substitute to conventional drug delivery systems.

This work was carried out for the development of FDDS with sustained-release of Glipizide using HPMC K-grade and Xanthan gum. The formulations showed promising sustained-release floating matrix tablets of Glipizide. Being obvious, HPMC K15M shown better retardation as compare to HPMC K 4M due to higher viscosity grade. High concentrations of higher viscosity-grade polymers induced the creation of stronger viscous-gel, which retarded the water penetration rate in the tablet matrices, that might resulted in the extended drug release. Polymer to drug ratio 2:1 shown better retardation due to higher concentration of polymers, while polymer to drug ratio 1:1 was unable to retard the release for 12hrs. When HPMC-K15 M and HPMC-K4 M used in ratios of 9:1 with xanthan gum, they shown more retardation and less than 75 % drug released in 12hrs, but when these polymers used in ratio 1:1 with xanthan gum shown better control over release pattern of the drug.