Chapter VIII
Summary & Conclusion

SUMMARY & CONCLUSION

The present study was aimed at formulating novel formulations for a low dose drug having high solubility and site specific absorption which can provide higher bioavailability compared to marketed extended release formulation. In order to achieve this, different polymers and different strategies, with different mechanisms for gastric retention were evaluated. Floating drug delivery is mainly developed either by incorporating a gas generating agent or by compressing at low hardness with low density excipients. Gas generating system has the disadvantage that there is a lag time in floating during which it may empty out of stomach. Un-coated tablets at low hardness have the disadvantage that its friability is high. In order to overcome this, non-gas generating floating system using low density excipients, having low hardness, and then coated with multiple layers (seal coated, drug coated and further polymer coated) to control the release profile was formulated. The advantage of this formulation was high rigidity and immediate floating property in water. Another formulation developed was by adopting Size exclusion technology (non –swelling) where immediate release (IR) tablet was coated with Ammonio methacrylate copolymer type B (RSPO) and Ammonio methacrylate copolymer type A (RLPO). Size exclusion (Swelling controlled) type tablets were also formulated with a combination of two polymers (Polyethylene oxide and Povidone) along with Hypromellose.

Gastric retention time was evaluated for all three approaches by embedding Barium Sulphate mini tablets as radio-marker in optimized formulations and following its movement in GI tract by X-Ray studies. In order to confirm the integrity of the tablets, two mini tablets containing barium sulphate were embedded in the formulation and were administered. By observing that the distance between the two barium sulphate tablets was not altered throughout the study by x-ray, it was confirmed that the integrity of the tablet is maintained. The study was performed in fed as well as fasted condition on healthy volunteers. It was found that integrity of the tablet was maintained throughout the study in all the formulations prepared by three approaches and no discomfort was reported by the volunteers confirming their safety for oral administration. Retention time found to be significantly high in fed condition compared to fasted condition. In fed condition, the retention time was best in Size exclusion (swelling controlled) approach. Also the variability was found to be least. Floating drug delivery was found to be highly variable.

Size exclusion (Non –swelling) type GR system was subjected to Biostudy. The plasma levels were found to be significantly low compared to marketed formulation. Reasons for low levels were investigated by trying to develop IVIVC by performing in- vitro dissolution profile in various buffers. pH 3.0 acid- base buffer found to be the bio-relevant media for IVIVC as lag time was observed in both the in vitro and in-vitro profile .

Swelling controlled drug delivery was tried with two different strategies; one with a combination of Hypromellose and Polyethylene oxide and the other with a combination of Hypromellose and Povidone (K-90). These formulations were optimized with different

release profiles and were evaluated against marketed preparation in healthy volunteers in fasted and fed state. Formulations with combination of Hypromellose and Polyethylene oxide showed supra bioavailability compared to the marketed formulation. The reason for it may be due to higher retention time in the stomach in case of Hypromellose – Polyethylene Oxide combination. Two formulations with combination of Hypromellose and Povidone showed comparable bioavailability compared to that of the marketed preparation. In order to establish in IVIVC of HPMC and PEO formulation, dissolution profile was carried out in various media, at various rpm, using different apparatus but no IVIVC could be established. However Level B correlation was established with HPMC and PVP combination.

It was also observed that bioavailability was higher in all the formulations in the fed state as compared to fasted confirming the hypothesis of directly proportional bioavailability with respect to gastro-retention time.

The non-bioavailable drug might be getting excreted through the faeces which is also reported in the literature (Following oral administration of ^{14}C – labeled alfuzosin solution, the recovery of radioactivity after 7 days, expressed as percentage of the administered dose, was 69% in feces and 24% in urine; CDER, Application no. 21-287).Since it was reported in the literature, it was decided not to go for quantification of drug in faeces in our studies.

Although much of the data available in the literature predict higher absorption of Alfuzosin HCl in the proximal part of small intestine (Maggi et al., 2000; Andrieu et al., 1995) no supporting data was available till date. Hence, single intestinal perfusion study was conducted to determine the permeability of the drug and closed loop method was employed to investigate the site of absorption. Our results showed that Alfuzosin has moderate absorption and more of it is absorbed through the ileum than duodenum. This data is in accordance with that reported by Abdenour Haddouche et al., (1996) based on their study conducted using ussing chamber.

It is observed that drug is permeated both from the duodenum and ileum but permeation is the rate limiting step. As per the report, the Absorption Number (small intestinal transit time / small intestinal absorption time) calculated by GastroPlus (Simulations Plus, Inc.) is 0.54 for Alfuzosin. Therefore, the mean time for absorption of Alfuzosin would be longer than the mean small intestinal transit time (PharmPK Discussion, 2006). Hence, it is hypothesized that in order to achieve maximum bioavailability; the rate of drug release should match with the rate of drug permeation from the absorption window.

Finally, scale- up parameters were optimized for the formulation that showed performance most near to the marketed preparation. Stability was evaluated according to ICH guidelines and was found to be stable.