CHAPTER IX

SUMMARY AND CONCLUSIONS

The thesis describes studies carried out on the design and evaluation of gastro-retentive (floating) tablets of pioglitazone employing olibanum, cross-linked starch urea and HPMC K15M. Introduction and objectives of the investigations are described in Chapter I. The real issue in the development of oral drug delivery systems is to prolong the residence time of the dosage form in the stomach or upper g.i.tract until the drug is completely released and absorbed. Several approaches are currently used to retain the dosage form in the stomach. These include bioadhesive systems, swelling and expanding systems, floating systems and other delayed gastric emptying devices. The principle of floating tablets offers a simple and practical approach to achieve increased gastric residence time to enhance the bioavailability and to obtain controlled release. Floating tablets are designed based on gas generating principle. Design of floating tablets needs a strong matrix former. Though several polymers are available for floating tablets, there is a continued need to develop new, effective and efficient polymers for controlled release floating tablets.

In the present investigation two new polymers namely (i) Olibanum (a natural gum-resin) and (ii) Cross-linked starch urea (a modified starch) were evaluated as matrix formers in the design of controlled release floating tablets in comparison to a widely studied polymer, HPMC K15M. The major objective of the investigation is to design and evaluate controlled release floating tablets of pioglitazone (an anti-diabetic drug) employing the above mentioned new and known polymers. The specific objectives of the investigation are (i) to design and evaluate floating tablets of pioglitazone based on gas...
generation principle employing sodium bicarbonate as gas generating agent and beeswax and ethyl cellulose as floating enhancers. (ii) to make a comparative evaluation of olibanum, cross-linked starch urea and HPMC K15M as matrix formers for controlled release floating tablets. (iii) to prepare and evaluate floating tablets of the selected drug for various physical properties and floating characteristics. (iv) to evaluate the drug release kinetics and mechanism of the floating tablets prepared. (v) to develop controlled release floating tablets of pioglitazone for once-a-day (24 hrs) administration. (vi) to evaluate the stability of floating and drug release characteristics of selected promising formulations. (vii) Pharmacokinetic evaluation of selected floating tablet formulations of pioglitazone developed in rabbits.

An overview of floating drug delivery systems is given in Chapter II. Literature on drug investigated i.e. pioglitazone and past work on gastro retentive and controlled release drug delivery systems of pioglitazone are given in Chapter III. Polymers investigated for application in floating tablets are described in Chapter IV. Olibanum and HPMC K15M were procured from commercial sources. Cross-linked starch urea was prepared in the laboratory. The preparation and characterization of cross-linked starch urea are described in Chapter IV. Starch urea cross-linked with calcium was prepared by gelatinizing potato starch in the presence of urea and calcium chloride. FTIR spectra of cross-linked starch urea indicated the presence of α- amylase and urea in the polymer. Melting point and DSC of cross-linked starch urea indicated charring of the compound at 220°C. Cross-linked starch urea consists of rectangular, transparent crystals. It was insoluble in water, aqueous fluids of acidic and alkaline pHs. Cross-linked starch urea exhibited good swelling in water. The swelling index was 740 %. All micromeritic
properties indicated good flow and compressibility needed for solid dosage form manufacturing. As cross-linked starch urea is insoluble in aqueous fluids of acidic and alkaline pHs and has good swelling property in water, it is considered suitable as release retarding and rate controlling polymer in floating tablets for controlled release.

Analytical methods employed are described in Chapter V. U.V spectrophotometric method was used for the estimation of pioglitazone in \textit{in vitro} studies. A known HPLC method was used for the estimation of pioglitazone in plasma samples.

Studies carried out on the formulation and evaluation of gastro retentive floating tablets of pioglitazone were described in Chapter VI. Floating tablets of pioglitazone were formulated employing (i) Olibanum (ii) Cross-linked starch urea and (iii) HPMC K15M as rate controlling matrix formers and sodium bicarbonate as gas generating agent. A total of 18 floating tablet formulations of pioglitazone were prepared employing sodium bicarbonate as gas generating agent at 15% and 20% strength in the tablets, beeswax (15%) and ethyl cellulose (5%) as floating enhancers. All the matrix tablets prepared were evaluated for hardness, friability, floating characteristics, disintegration and drug release characteristics. From the results obtained the following conclusions are drawn.

1. The floating tablets prepared were non-disintegrating in water and aqueous fluids of acidic pH (1.2) and alkaline pH (7.4).
2. All the floating tablets prepared employing olibanum, cross-linked starch urea and HPMC K15M were of good quality with regard to drug content, hardness and friability.
3. The floating characteristics of the formulations, which contain sodium bicarbonate (15%) alone were not satisfactory with all the three polymers and need to be improved.

4. Beeswax and ethyl cellulose, which are lipophilic materials having density less than one, were tried to decrease the hydrophilic property of the formulation to increase the buoyancy.

5. When beeswax (15%) was incorporated in the formulations the floating time was in the range 23-42 h and the floating lag time was in the range 2-11 min.

6. Formulations containing sodium bicarbonate (15%), beeswax (15%) and ethyl cellulose (5%) exhibited excellent floating characteristics. Floating time was in the range 44-48 h and floating lag time was 1-3 min with HPMC; 4-7 min with cross-linked starch urea and 5-6 min with olibanum. Floating characteristics of matrix tablets formulated with olibanum and cross-linked starch urea are comparable with those of tablets formulated with HPMC K15M.

7. Overall, increasing the strength of sodium bicarbonate from 15% to 20% has not much improved the floating characteristics. Addition of beeswax (15%) and ethyl cellulose (5%) has significantly enhanced the buoyancy of the tablets formulated with all the three polymers.

8. Pioglitazone release from all the floating tablets prepared was slow and spread over 24 h and depended on the polymer used and composition of the tablets.

9. Pioglitazone release from all floating tablets was diffusion controlled and followed zero order kinetics.
10. Non-fickian (anamalous) diffusion was the release mechanism from all the floating tablets prepared with various polymers.

11. Pioglitazone release from the tablets containing sodium bicarbonate, beeswax and ethyl cellulose along with the matrix forming polymers was slow and spread over 24 h. The $T_{90}$ values were in the range 19 – 24 h with these tablets. These tablets also exhibited good floating characteristics apart from controlled drug release over 24 h.

12. Based on the release characteristics of floating tablets PF7, PF8 and PF9, which contain sodium bicarbonate (15%), beeswax (15%), ethyl cellulose (5%), the order of release retarding efficiency of various polymers was olibanum > cross-linked starch urea > HPMC (based on $K_0$).

13. Based on the release characteristics of tablets PF16, PF17 and PF18 which contain sodium bicarbonate (20%), beeswax (15%) and ethyl cellulose (5%), the order of release retarding efficiency of various polymers was olibanum > cross-linked starch urea = HPMC (based on $K_0$).

Studies on pharmacokinetic evaluation of pioglitazone floating tablets formulated employing olibanum, cross-linked starch urea and HPMC K15M are described in Chapter VII. Pharmacokinetic evaluation was done on pioglitazone floating tablets formulated employing various matrix formers in comparison to pioglitazone pure drug in rabbits with a view to evaluate the *in vivo* performance of the three polymers proposed for floating tablets. Pioglitazone pure drug and its floating tablets were tested at a dose of 10 mg in rabbits. The study was conducted as a crossover RBD in healthy rabbits of
either sex (n = 6) with a washout period of one month. Plasma concentrations of pioglitazone were determined by a known HPLC method.

The results obtained indicated the following:

1. The elimination rate constant ($K_{el}$) for pioglitazone was 0.1199 h$^{-1}$ and the corresponding biological half life was 5.78 h following the oral administration of pioglitazone. The mean residence time (MRT) was found to be 9.82 h. The absorption rate constant ($K_a$) was found to be 1.462 h$^{-1}$. A $C_{max}$ of $5.7 \pm 0.19 \mu g/ml$ was observed at 3.0 h after oral administration of pioglitazone pure drug. Later the plasma concentrations were decreased rapidly.

2. The absorption of pioglitazone was slow from all the three floating tablets formulated. A $C_{max}$ of $3.7 \pm 0.12 \mu g/ml$, $3.8 \pm 0.17 \mu g/ml$ and $3.1 \pm 0.51 \mu g/ml$ was observed at 6.0 h following the oral administration of floating tablets formulated employing olibanum (B), cross-linked starch urea (C) and HPMC K15M (D) respectively. The absorption rate constant ($K_a$) was found to be 0.133 h$^{-1}$, 0.225 h$^{-1}$ and 0.1598 h$^{-1}$ for floating tablets B, C and D respectively.

3. The mean residence time (MRT) was increased from 9.82 h for pioglitazone pure drug (A) to 13.65 h, 13.48 h and 13.30 h respectively with the floating tablets B, C and D. Based on $\mathrm{AUC}_{0-\infty}$ the relative bioavailability of pioglitazone from the floating tablets was found to be 102.05 %, 92.52% and 90.58% respectively with floating tablets B, C and D when compared to pioglitazone pure drug (100 %).

4. The pharmacokinetic evaluation, thus, indicated that pioglitazone from the floating tablets was released and absorbed slowly over longer periods of time.
in vivo resulting in the maintenance of plasma concentration within a narrow range over a longer period of time.

The stability of selected floating tablet formulations developed employing (i) olibanum (ii) cross-linked starch urea (iii) HPMC K15M was evaluated as per ICH guidelines for accelerated testing. These studies are described in Chapter VIII. No visible changes were observed in the floating tablets after storage. No significant difference (P > 0.05) was observed in the percent drug content before and after storage for 6 months. No difference was observed in the floating lag and floating time of the tablets. The drug release characteristics of all the formulations tested remained unaltered during the storage period. The drug content, floating characteristics and drug release rate of the floating tablets formulated employing (i) olibanum (ii) cross-linked starch urea and (iii) HPMC K15M were quite stable. The controlled release characteristics of the floating tablets remained unaltered.

SIGNIFICANT CONTRIBUTIONS AND RECOMMENDATION:

The present investigation, thus, resulted in the development of two new polymers namely (i) olibanum (natural gum-resin) and (ii) cross-linked starch urea (a modified starch) as matrix formers for controlled release floating tablets. The floating and drug release characteristics of pioglitazone floating tablets formulated employing olibanum and cross-linked starch urea were comparable to those formulated employing HPMC K15M. Tablets with a floating time of 44 h after a lag time of 2-6 min could be designed employing these two new polymers along with sodium bicarbonate, beeswax, and ethyl cellulose. The floating tablets formulated employing olibanum and cross-
linked starch urea exhibited good controlled release characteristics \textit{in vitro} and \textit{in vivo}. The floating and controlled release characteristics of these floating tablets remained unaltered during short term accelerated stability testing. Hence, olibanum and cross-linked starch urea are recommended as matrix formers for the design of controlled release floating tablets.