CHAPTER I

INTRODUCTION AND OBJECTIVES OF THE INVESTIGATION

The oral route of drug administration is the most convenient and commonly used method of drug delivery. However, this route has certain problems such as unpredictable gastric emptying rate, short gastro intestinal transit time (8-12h) and existence of an absorption window in the gastric and upper small intestine for several drugs\textsuperscript{1,2} leading to low and variable oral absorption over shorter period of time. 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\textsuperscript{3}, swelling and expanding systems\textsuperscript{4, 5}, floating systems\textsuperscript{6, 7} and other delayed gastric emptying devices\textsuperscript{8, 9}.

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 forming former. Several polymers such as various viscosity grades of HPMC, Carbopol 934P, Eudragit RL, calcium alginate, chitosan, xanthan gum, guargum, ethyl cellulose etc., have been used in the design of floating tablets of various APIs. Though these 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.

Olibanum is a natural gum resin obtained from *Boswellia serrata*, Roxburgh and other species of *Boswellia*. Olibanum consists \(^\text{10}\) chiefly an acid resin (50-60%), gum (30-36%) and volatile oil (3-8%). The resin contains \(^\text{11}\) mainly a resin acid (boswellic acid) and a resene (olibanoresene) in equal proportions. Chowdary, et al. \(^\text{12-19}\) reported first time olibanum gum and resin as efficient matrix formers and microencapsulating agents for controlled release.

Modified starches are promising and having good potential as release retardants and rate controlling polymers for controlled release. Cross-linked starch urea is a modified starch prepared by gelatinization of starch in the presence of urea and cross linking by treatment with calcium chloride. The cross linked polymers generally swell in water and aqueous fluids to form gelatinized matrices suitable for controlled release. Cross-linked starch urea is reported \(^\text{20, 21}\) as an efficient rate controlling matrix former for controlled release.

The major objective of the investigation is to design and evaluate controlled release floating tablets of pioglitazone employing the above mentioned new and known polymers.

Pioglitazone is an effective oral anti-diabetic agent that belongs to the thiazolidone diones drug class and is widely prescribed in the management of non-insulin dependent (Type II) diabetes mellitus. It is poorly soluble in aqueous fluids and is majorly absorbed from stomach \(^\text{22}\). Dosage forms that are retained in the stomach would increase its oral bioavailability and efficacy. Pharmacological studies indicate that
pioglitazone improves glycemic control while reducing circulating insulin level\textsuperscript{23}. Pioglitazone has short biological half-life of 3-6 hours and is eliminated rapidly.\textsuperscript{24} Therefore control release (CR) products are needed for pioglitazone to prolong its duration of action and to improve patient compliance. Controlled release formulation is needed for pioglitazone for better control of blood glucose levels to prevent hypoglycemia and to enhance their clinical efficacy and patient compliance. Floating tablets of pioglitazone are designed employing Olibanum, Cross-linked starch urea and HPMC K15M with an objective of enhancing its oral bioavailability and to achieve controlled release.

The specific objectives of the investigation are as follows:

1. 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.

2. To make a comparative evaluation of (i) Olibanum and (ii) Cross-linked starch urea and (iii) HPMC K15M as matrix formers for controlled release floating tablets.

3. To prepare and evaluate floating tablets of the selected drug for various physical properties and floating characteristics.

4. To evaluate the drug release kinetics and mechanism of the floating tablets prepared.

5. To develop controlled release floating tablets of pioglitazone for once-a-day (24 hrs) administration.
6. To evaluate the stability of floating and drug release characteristics of selected promising formulations.

7. Pharmacokinetic evaluation of selected floating tablet formulations of pioglitazone developed in rabbits.

Extensive experimentation, both *invitro* and *invivo* has been carried out to fulfill the objectives of the investigation and the studies carried out and the results obtained are described in the subsequent chapters.
REFERENCES


