Chapter 1

Introduction
INTRODUCTION

The primary aim of oral controlled drug delivery system is to achieve better bioavailability and release of drug from the system, which should be predictable and reproducible. But this is difficult due to number of physiological problems such as fluctuation in the gastric emptying process, narrow absorption window and stability problem in the intestine. This can be overcome by altering the physiological state and designing the formulations, by which gastric emptying process can be extended from few minutes to 12 h. A drug can act locally in the stomach in case of H. Pylori (tetracycline) or in the proximal part of the intestine by prolonged contact with absorbing area.\(^1,2\) Prolonged gastric retention increases bioavailability, decreases wastage of drugs, increases solubility of drugs, which are less soluble in alkaline pH.\(^3\) These dosage forms prolongs the gastric residence time enabling an extended absorption phase for the local treatment of drugs and better bioavailability for the drugs that are unstable in intestinal or colonic environment.\(^4,5\) Gastric retention can be achieved by mucoadhesion or bioadhesion systems,\(^6\) expansion systems,\(^7,8\) high density systems,\(^9,10,11\) magnetic systems,\(^12,13,14\) superporous hydrogels,\(^15,16\) raft forming systems,\(^17,18,19\) low density systems,\(^20,21,22\) and floating ion exchange resins.\(^23\)

Losartan potassium is an orally active non-peptide angiotensin II receptor (type AT1) antagonist used in the treatment of hypertension due to blockade of AT1 receptors. It is readily absorbed from the stomach and upper part of small intestine. The main limitation which causes low therapeutic effectiveness is due to narrow absorption window, poor bioavailability (25-35 %) and short biological half life (1.5-2 h). Conventional tablets should be administered 3-4 times to maintain plasma drug concentration. To increase therapeutic efficacy, reduce frequency of administration and for better patient compliance, twice daily-sustained release Losartan potassium
gastroretentive dosage forms are prepared. Losartan potassium belongs to the class III of BCS (Biopharmaceutical classification of system), exhibiting high solubility and low permeability. Hence, enhanced gastric retention time of Losartan potassium controlled release dosage form will increase its absorption. Therefore, Losartan potassium was selected as a suitable drug for designing gastroretentive drug delivery system (GDDS) with a view to improve its oral bioavailability.

Verapamil hydrochloride, a calcium channel blocker, is weakly basic in nature and demonstrates poor bioavailability in the small intestine because of pH-dependent solubility (poorly soluble at high pH values, highly soluble at low pH values). In medical practice, it is most widely used in conventional tablet form with a minimal dose of 40 mg and a maximal dose of 180 mg, and for slow release doses ranges between 120–240 mg. Only 10–20 % of total dose absorbed from the digestive tract penetrates to the systemic circulation in an unchanged form. This is due to the narrow absorption window of the drug.

Rosiglitazone maleate (RGM) is an antidiabetic drug for type II diabetes that improves insulin sensitivity in muscle and adipose tissues through activation of peroxisome proliferator-activated γ-receptor (PPARγ) that are involved in transcription of insulin-responsive genes responsible for glucose production, transport, and utilization. The drug shows linear pharmacokinetics over a dose of 0.2–20 mg with biological half-life of 3–4 h with oral bioavailability of 99.8%. The drug is highly soluble in simulated gastrointestinal fluid (SGF). But the solubility gradually decreases with increment of pH above 7. Therefore, the rate and extent of absorption viz. bioavailability of the drug is mainly controlled by its dissolution rate. Following rosiglitazone therapy for 8 to 12 weeks, the dose should be increased to 8 mg/day in case of insufficient glycemic control, which results in higher incidents of
dose-dependent side effects such as gastrointestinal disturbances, headache, altered blood lipids, edema, and hypoglycaemia.

The present study envisages the designing and development of pharmaceutical dosage forms with gastric floating property to improve the bioavailability of above drugs.
NEED FOR THE STUDY

Oral drug delivery still remains user friendly form, having the highest degree of patient compliance, and highly preferred route of drug administration. As such, drug for chronic condition are often administered orally for ease of long term use. The peroral dosage form cannot achieve prolongation of effective plasma concentration and effective bioavailability due to the changing environment in the GIT. This is because of various physiological problems like gastric emptying, motility, pH of the stomach etc.

This can be overcome by developing suitable dosage form that could be retained in the stomach for prolong period. Drugs having narrow absorption window, stability problem and which need to act locally in stomach can be formulated as a floating drug delivery system.

Such systems improve bioavailability, enhances absorption despite first pass effect, avoid the fluctuation in plasma drug concentration and maintain desirable level by continuous drug release. It also improves patient compliance by reducing dosing frequency and decrease wastage of drug. The multiple particulate unit dosage forms are more reliable and are freely distributed throughout GI tracts as compared to single unit formulation, which suffers “all or none concept”.

The drugs selected for the present work have low solubility at higher pH and narrow absorption window. Hence gastric floating drug delivery systems like hollow microspheres and tablets were designed to retain in the stomach. The systems were prepared to improve the bioavailability and achieve steady-state plasma concentration of the drug. In the present work an attempt is made to design and formulate dosage forms like effervescent floating tablets, hollow microspheres and non-effervescent floating tablets system using different polymer to improve the
bioavailability and achieve steady-state plasma concentration of the verapamil hydrochloride, rosiglitazone maleate and losartan potassium respectively.