AIM AND OBJECTIVE OF THE PRESENT INVESTIGATION

An orally administered controlled drug delivery system encounters a wide range of highly variable conditions, such as pH, agitation intensity and composition of the gastrointestinal fluids as it passes down the gastrointestinal tract (GIT). Ideally, an oral controlled drug delivery system releases the drug at a constant and reproducible rate despite varying conditions. Many efforts have been made to design oral controlled drug delivery systems that deliver the drug at a constant rate as it passes down the GIT. In spite of constant rate of release of drug from the dosage form it may not be absorbed uniformly over the length of the GIT. Drug absorption from the colon is usually erratic and inefficient and also, certain drugs get absorbed only from the stomach or the upper parts of the small intestine.

Furthermore, an important factor which may adversely affect the performance of an oral controlled drug delivery system is the gastric transit time. More particularly, in instances where the drug has clear-cut “absorption window” i.e., the drug is absorbed only from the specific regions of the stomach or upper parts of the small intestine, absorption may not be complete with a typical oral controlled drug delivery system in which it is rapidly transported due to less gastric transit time. It is apparent that, for a drug exhibiting “absorption window”, an effective oral controlled drug delivery system is needed not only to deliver the drug at a controlled rate but also to retain the drug in the upper parts of the GIT for a long period of time.
Various approaches have been made to retain the dosage form in stomach as a way to increase the overall gastric retention time which include high density systems\(^1\), floating systems\(^2-5\), expandable, unfoldable and swelling systems\(^6-8\), super porous hydrogels\(^9\), bioadhesive systems\(^10,11\), magnetic systems\(^12\), osmotic regulated systems and use of passage delaying agents\(^13\).

Out of these approaches, gastric floating drug delivery is considerably an easy and logical approach in the development of gastric floating drug delivery systems (GFDDS). These systems have density lower than gastric fluids (normally less than one) and remain buoyant in the stomach contents which seem to be useful for drugs primarily absorbed in the stomach, duodenum, and upper jejunum segments. The GFDDS are able to prolong the retention time of a dosage form in the GIT, thereby improving the oral bioavailability\(^14\). However, these GFDDS are suitable for delivery of drugs over a period of 12 hours as the gastric retention of any material lasts normally for a period of 6-10 hrs\(^15-17\).

GFDDS are broadly classified into two major groups, namely effervescent and non-effervescent systems. Effervescent systems contain hydrocolloids or hydrophilic polymers along with carbonates or bicarbonates. These polymers swell on contact with gastric fluids. The incorporated carbonates or bicarbonates react with gastric acid or any other acid (e.g., citric acid or tartaric acid usually incorporated in the dosage form) present in the formulation to produce CO\(_2\). The generated carbon dioxide is entrapped into swollen gel matrix layer and thus
reducing the density of the system and keeping it afloat in stomach fluids.

The capacity of the swollen gel matrix to retain the generated carbon dioxide plays an important role in deciding the floating time and efficiency of the prepared GFDDS. Hence number of hydrophilic polymers with good swelling property from synthetic, semi synthetic and natural origin like Eudragit, polyvinyl acetate, povidone, hydroxylpropyl methyl cellulose (HPMC), hydroxylpropyl cellulose (HPC), carrageenans, hupu gum, guar gum etc., were earlier studied on the formulation of GFDDS.

Non-effervescent floating systems usually contain one or more hydrocolloids along with drug and other additives like fatty excipients. Non-effervescent approaches of matrix tablets involves porosity enhancement, entrapment of swollen particles of superdisintegrant in gel matrix\textsuperscript{18}, addition of low-density excipients in formulation, such as polypropylene foam powder or aerosil and use of high content of hydrophobic compounds\textsuperscript{19}. These systems achieve immediate floating because of the low density of the system without any floating lag time.

Famotidine, a histamine H\textsubscript{2}-receptor antagonist, is widely used in active duodenal ulcers, gastric ulcers, Zollinger-Ellison syndrome, gastro oesophageal reflux disease and erosive oesophagitis\textsuperscript{20}. The plasma half life of the drug is 2.5-3.5 hrs as reported in literature, hence multiple doses are needed. which leads to patient incompliance and fluctuations in plasma concentration\textsuperscript{21}. The recommended adult oral dose of famotidine is 20 mg twice daily or 40 mg once daily. The
effective treatment of erosive oesophagitis requires administration of 20 mg of famotidine 4 times a day. Gastric acid secretion in case of ulcers cannot be inhibited beyond 5 hrs with a conventional dose of 20 mg of famotidine. An alternative dose of 40 mg leads to plasma fluctuations; thus a sustained release dosage form of famotidine is desirable.

Additionally, famotidine is not absorbed uniformly throughout the gastrointestinal tract (GIT) but mainly at a specific absorption site (stomach and upper part of small intestine)\(^2^2\) leading to incomplete and variable absorption (bioavailability is 40-50\%)\(^2^3\). Thus, a dosage form achieving gastric retention, thereby presenting the system at absorption site over a prolonged period is beneficial for improving bioavailability, minimizing wastage and side effect is highly desirable\(^2^4\). Moreover, being a weak base, famotidine with a \(pK_a\) of 7.06 has pH dependant solubility (maximum solubility at acidic pH) and its gastric retention would allow adequate time for its dissolution, the rate limiting step in drug absorption\(^2^4\)\,-\(^2^6\). In view of these unique absorption characteristics, the gastric residence time of famotidine formulation should be prolonged to permit famotidine to reach the site of absorption in a controlled manner so as to increase its oral bioavailability. Hence famotidine was chosen as a drug of choice for developing GFDDS with both effervescent and non-effervescent approaches.

PEO, a nonionic homopolymer of ethylene oxide, is available in different molecular grades. PEOs are mostly used to produce controlled release solid dosage forms such as matrices, reservoirs or coated
PEOs control the release of the active moiety either by swelling (large molecular weight, >2 MDa) or by eroding and swelling (small molecular weight, <0.9 MDa), forming a hydrogel in water. It has physical and chemical stability, good compressibility, high swelling ability, and good solubility in water. There are only few reports on the use of PEO in the design of GFDDS and no reports in the development of famotidine GFDDS. Hence, PEO is proposed for the development of effervescent gastric floating matrix tablets (EGFMT). As molecular weight of PEO is critical in the control of drug release two grades of PEO (WSR 303 and WSR N-12K) are chosen for the design of EGFMT of famotidine. The molecular weight of WSR 303 and WSR N-12K are 7 MDa and 1 MDa respectively. The viscosity of the PEO depends on the molecular weight and the viscosity of WSR 303 for 1% solution is 7,500–10,000 cps and that of WSR N-12K is 400-800 cps (for 2% solution).

Glyceryl behenate (GB) is an insoluble, non-swelling, matrix forming wax material. It is a mixture of glycerides of fatty acids, mainly behenic acid, originally introduced as a lubricant in tablet and capsule manufacturing. It has been used in the preparation of sustained release tablets and as a matrix forming agent for the controlled release of water soluble drugs. It is having a density of 0.942 g/cm³ which is less than the density of gastric fluids. There are no reports on the use GB for the development of GFDDS. Hence it is proposed to study its applicability in the design of non effervescent gastric floating matrix
tablets (NEGFMT) of famotidine because of its capability to control drug release as well as low density of the polymer.

The main aim of the present investigation is to design GFDDS of famotidine using two approaches i.e. effervescent and non-effervescent by using PEO and GB respectively for releasing the drug over a period of 12 hrs.

The major objectives of the investigation are as follows.

1. To study the applicability of the two grades of PEOs in the design of EGFMT of famotidine using sodium bicarbonate as gas generating agent.
2. To study the applicability of GB in the design of NEGFMT of famotidine.
3. Calculation of immediate and maintenance doses of the famotidine for proposed EGFMT and NEGFMT and prediction of theoretical profile.
4. Optimization of prepared EGFMT and NEGFMT for the release of famotidine over a period of 12 hrs.
5. Optimization of polymer concentration, effervescent agent concentration and other ingredients based on the evaluation parameters like floating lag time, floating time and matching of drug release profile with the theoretical profile using statistical optimization technique like response surface methodology in full factorial design.
6. To carry out drug and excipient interaction studies of the optimized product and their stability as per ICH guidelines.
7. To carry out the \textit{in vivo} floating ability of the selected optimized GFMT by X-ray evaluation.

8. To study the \textit{in vivo} performance of the selected optimized GFMT.

The results are presented and discussed in the subsequent chapters with the help of appropriate references at the end of each chapter.
REFERENCES


