DESIGN AND DEVELOPMENT OF FLOATING DRUG DELIVERY SYSTEM OF RANITIDINE & GLIPIZIDE

1 Introduction
Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting good in vitro floating behavior show prolonged gastric residence in vivo\(^1,2\). The physical properties of the drug delivery system (e.g., density and size) as well as the presence of food in the stomach have been identified as the two most important parameters determining the in vivo performance of the dosage form\(^3\). Under fasted conditions the stomach is cleared of undigested material every 1.5 to 2 h by housekeeper waves. To provide good floating behavior in the stomach, the density of the device should be less than that of the gastric contents (\(\approx 1.004\) g/cm\(^3\)).

However, it has to be pointed out that good in vitro floating behavior alone is not sufficient proof for efficient gastric retention in vivo. The effects of the simultaneous presence of food and of the complex motility of the stomach are difficult to estimate. Obviously, only in vivo studies can provide definite proof that prolonged gastric residence is obtained\(^4\).

Extended-release dosage forms with prolonged residence times in the stomach are highly desirable for drugs (i) that are locally active in the stomach, (ii) that have an absorption window in the stomach or in the upper small intestine, (iii) that are unstable in the intestinal or colonic environment, and/or (iv) have low solubility at high pH values. In addition, as the total gastrointestinal transit time of dosage forms is increased by prolonging the gastric residence time, these systems can also be used as sustained release devices with a reduced frequency of administration and, therefore, improved patient compliance. Recent approaches to increase the gastric residence time of drug delivery systems include (i) bioadhesive devices, (ii) systems that rapidly increase in size upon swallowing, and (iii) low density devices that float on the gastric contents\(^5-9\).

Floating tablets containing a mixture of drug and hydrocolloids that remain in the stomach for an extended period of time have been described\(^10,11\). Matrix tablets based on hydroxy-propyl methylcellulose (HPMC K4M) have been developed by Baumgartner et al.\(^12\). Upon contact with gastric fluid, the systems take up water and swell. As the increase in volume is greater than the increase in mass during swelling, the densities of these devices decrease and the systems start to float after a short lag time. The influence of different processing and formulation parameters on the floating properties of matrix tablets has been studied\(^13-16\).
An interesting approach to provide floating drug delivery systems is based on the formation of carbon dioxide within the device upon contact with body fluids. Multi-layer matrix tablets have been described containing an effervescent layer with carbonate and, optionally, citric acid\textsuperscript{17,18,19}. Upon contact with acidic aqueous media, carbon dioxide is generated and entrapped within the gelling hydrocolloid, causing the system to float. Timmermans and Moës\textsuperscript{20} quantified the floating capabilities of matrix systems based on swellable polymers, including gas-generating systems. However, long-term floating behavior is not observed with any of the investigated dosage forms.

A floating drug delivery system, being less dense than gastric juice due to the incorporation of at least one porous structural element, such as foam or a hollow body, is described by Müller and Anders\textsuperscript{21}.

Different mass transport processes may occur during drug release from polymer-based matrix tablets, including (i) water imbibition into the system, (ii) polymer swelling, (iii) drug dissolution, (iv) drug diffusion out of the tablet, and (v) polymer dissolution. Depending on the type of drug, polymer and release medium and on the tablet composition, the respective processes are more or less important\textsuperscript{22,23}. Velasco et al.\textsuperscript{24} reported that the rate and mechanism of diclofenac sodium release from HPMC K15M-based matrices are mainly controlled by the drug/HPMC ratio, and that drug release is independent of the compression force in the range between 3 and 12 kN. The effects of the two formulation variables “HPMC/lactose ratio” and “HPMC viscosity grade” on the release of adinazolam mesylate from cylindrical tablets is studied by Sung et al.\textsuperscript{25}. The resulting drug release rate is found to increase with decreasing “HPMC/lactose ratio” and decreasing “HPMC viscosity grade”
1.1. **Advantages of floating dosage form**

- The Principle of HBS may not limited to any particular medicament or class of medicament
- The HBS formulations are not restricted to medicaments, which are absorbed from stomach, since it has been found that these are equally efficacious with medicament, which absorbed from the intestine.
- Acidic substances like aspirin cause irritation on the stomach wall when come in to contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
- The HBS are advantageous for drugs absorbed through the stomach. e.g. Ferrous salts, antacids.
- The efficacy of the medicaments administered utilizing the sustained release principle of HBS formulation has been found to be independent of the site of particular medicaments.
- The HBS are advantageous for drugs meant for local action in the stomach. e.g. Antacids.
- Administration of prolongs release floating dosage forms, tablet or capsules, will results in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from the floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
- When there is vigorous intestinal movement and a shorted transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.
1.2 Limitations/disadvantages of Floating Drug Delivery System

- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water.
- Not suitable for drugs that have solubility or stability problem in GIT.
- Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
- Drugs which are irritant to Gastric mucosa is also not desirable or suitable.
- The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
- The dosage form should be administered with a full glass of water (200-250 ml).
- These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract.

1.3 Application of floating drug delivery system

- Recent study indicated that the administration of Diltiazem floating tablets twice a day might be more effective compared to normal tablets in controlling the Blood pressure of hypertensive patients.
- Modapar® HBS containing L-Dopa and Benserazide, here the drug is absorbed over a period of 6-8 hours and maintained substantial plasma concentration for Parkinsonian patients. Cytotech®- containing Misoprostol, a synthetic prostaglandin –EL analogue, for prevention of gastric ulcer caused by non-steroidal anti-inflammatory drugs (NSAIDS).
- As it provides high concentration of drug within gastric mucosa, it is used to eradicate H. pylori (a causative organism for chronic gastritis and peptic ulcers).
- 5-fluorouracil has been successfully evaluated in the patients with stomach neoplasm.
- Developing HBS dosage form for tacrin provide better delivery systems and reduced its GI side effects.
- Treatment of gastric and duodenal ulcer.
1.4. **Basic physiology of the gastrointestinal tract**

Anatomically the stomach is divided into three regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the two states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myolectric cycle or migrating myolectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Ishington.

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

1.5. **Future potential**

- Floating dosage form offers various future potential as evident from several recent publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying.
- Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability.
- Buoyant delivery system considered as a beneficial strategy for the treatment of gastric and duodenal cancers.
- The floating concept can also be utilized in the development of various anti-reflux formulations.
• Developing a controlled release system for the drugs, which are potential to treat the Parkinson’s disease.

• To explore the eradication of Halico-bector pylori by using the narrow spectrum antibodies.