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STOMACH SPECIFIC FLOATING DRUG DELIVERY SYSTEM: A REVIEW

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Abstract : Technological attempts have been made in the research and development of rate-controlled oral drug delivery systems to overcome physiological adversities, such as short gastric residence times (GRT) and unpredictable gastric emptying times (GET). It is known that differences in gastric physiology, such as, gastric pH, and motility exhibit both intra-as well as inter-subject variability demonstrating significant impact on gastric retention time and drug delivery behaviour. This triggered the attention towards formulation of stomach specific (gastro retentive) dosage forms. This dosage forms will be very much useful to deliver 'narrow absorption window' drugs. Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), swelling and expanding systems, polymeric bioadhesive systems, high-density systems, modified-shape systems and other delayed gastric emptying devices. In this review, current & recent developments of Stomach Specific FDDS are discussed.

Keywords: gastric residence time, floating drug delivery system, hydrodynamically balanced system, effervescent, non-effervescent

Introduction

The high level of patient compliance in taking oral dosage forms is due to the ease of administration and handling of these forms. Although tremendous advances have been seen in oral controlled drug delivery system in the last two decades, this system has been of limited success in the case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). In the development of oral controlled drug delivery system, one of the main challenges is to modify the GI transit time. Gastric emptying of pharmaceuticals is highly variable and is dependent on the dosage form and the fed/fasted state of the stomach. Normal gastric residence times usually range between 5 minutes and 2 hours. In the fasted state the electrical activity in the stomach – the interdigestive myoelectric cycle or migrating myoelectric complex (MMC) governs the activity and, hence, the transit of dosage forms. It is characterized by four phases: Phase I–Period of no contraction (40-60 minutes), phase II –Period of intermittent contractions (20-40 minutes), phase III–Period of regular contractions at the maximal frequency that travel distally also known as housekeeper wave. (10-20 minutes) and phase IV–Period of transition between phase III and phase I (0-5 minutes) [1].

Gastric emptying is unpredictable if there are physiological problems and other factors like the presence of food. Drugs having a short half-life are eliminated quickly from the blood circulation. Various oral controlled delivery systems have been designed which can overcome these problems and release the drug to maintain its plasma concentration for a longer period of time.

This has led to the development of oral gastroretentive dosage forms. Gastroretention is essential for drugs that are absorbed from the stomach, drugs that are poorly

soluble or degraded by the higher pH of intestine, and drugs with an absorption which can be modified by changes in gastric emptying time. Gastroretentive dosage forms are also useful for local as well as sustained drug delivery for certain conditions, like H. pylori infection which is the cause of peptic ulcers. This dosage form improves bioavailability, therapeutic efficacy and may even also allow a possible reduction in the dose because of steady therapeutic levels of drug, for example furosemide and ofloxacin. The reduction in fluctuations in therapeutic levels minimizes the risk of resistance especially in case of β-lactam antibiotics (penicillins and cephalosporins) [2]

To formulate a successful stomach specific or gastroretentive drug delivery system, several techniques are currently used such as hydrodynamically balanced systems (HBS) / floating drug delivery system[3], low-density systems[4-6], raft systems incorporating alginate gels[7-9], bioadhesive or mucoadhesive systems[10], high density systems[11-13], superporous hydrogels[14] and magnetic systems[15-17].

Stomach Specific Floating Drug Delivery

Stomach Specific FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration.

The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems' ('HBS') since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3- 4 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents. Among the different hydrocolloids recommended for floating form formulations, cellulose ether polymers are most popular, especially hydroxypropylmethylcellulose (HPMC). Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy [18].

Parallel to formulation studies, investigations have been undertaken in animals and humans to evaluate the intragastric retention performances of floating forms. These assessments were realised either indirectly through pharmacokinetic studies with a drug tracer, or directly by means of X-ray and gamma scintigraphic monitoring of the form transit in the GI tract.

Mechanism of floating systems

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas-generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co-administration of gastric-emptying delaying drugs. Among these, the floating dosage forms have been most commonly used. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents (given in the Figure 1 (a)), the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side (Figure 1(b)). This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations [19]

$$F = F_{buoyancy} - F_{gravity}$$

$$= (Df - Ds)\, gv \text{--- (1)}$$

Where, F= total vertical force, Df = fluid density,

Ds = object density, v = volume and

g = acceleration due to gravity.

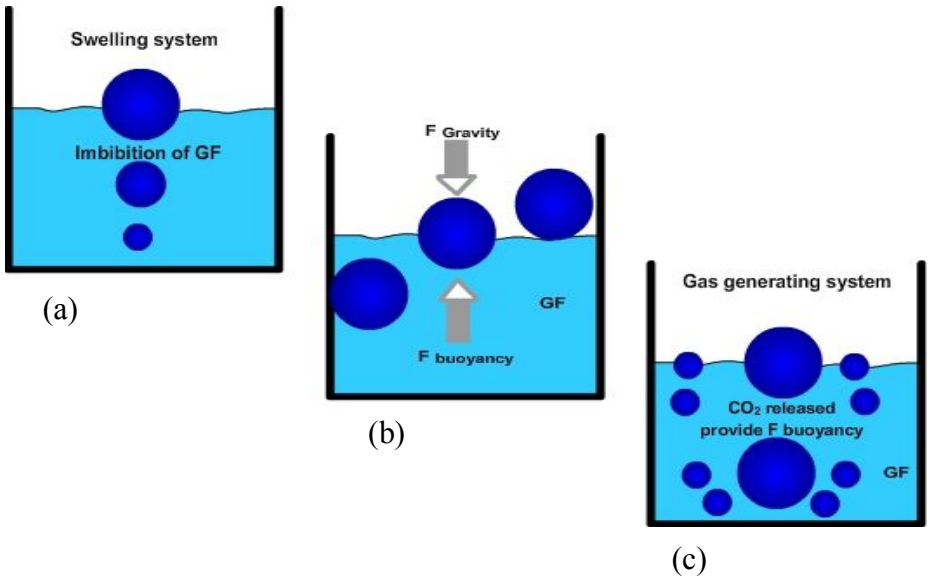

Fig.1. Mechanism of floating systems, GF= Gastric fluid

Based on the mechanism of buoyancy FDDS can be classified into

A. Single Unit Floating Dosage Systems
   a) Effervescent Systems (Gas-generating Systems)
   b) Non-effervescent Systems
B. Multiple Unit Floating Dosage Systems
   a) Non-effervescent Systems
   b) Effervescent Systems (Gas-generating Systems)
   c) Hollow Microspheres
C. Raft Forming Systems

A. Single Unit Floating Dosage Systems:

a) Effervescent Systems (Gas-generating Systems):

These buoyant systems utilised matrices prepared with swellable polymers like HPMC, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach [20].

Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, Carbopol®, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

Ozdemir *et al* [21] prepared floating bilayer tablets with controlled release for furosemide. The low solubility of the drug could be enhanced by using the kneading method, preparing a solid dispersion with β cyclodextrin mixed in a 1:1 ratio. One layer contained the polymers HPMC 4000, HPMC 100, and CMC (for the control of the drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid. Radiographic studies on 6 healthy male volunteers showed that floating tablets were retained in stomach for 6 hours and further blood analysis studies showed that bioavailability of these tablets was 1.8 times that of the conventional tablets. On measuring the volume of urine the peak diuretic effect seen in the conventional tablets was decreased and prolonged in the case of floating dosage form.

Penners *et al* [22] prepared an expandable tablet containing mixture of polyvinyl lactams and polyacrylates that swell rapidly in an aqueous environment and thus stays in stomach over an extended period of time. In addition to this, gas-forming agents were also incorporated so as soon as the gas formed, the density of the system was reduced and thus the system tended to float on the gastric environment.

Talwar *et al* [23] prepared a once-daily formulation for oral administration of ciprofloxacin. The formulation was composed of 69.9% ciprofloxacin base, 0.34% sodium alginate, 1.03% xanthum gum, 13.7% sodium bicarbonate, and 12.1% cross-linked poly vinyl pyrrolidine. The cross linked PVP initially and the gel-forming polymers later formed a hydrated gel matrix that entrapped the gas, causing the tablet to float and be retained in the stomach The hydrated gel matrix created a diffusion path for the drug, resulting in sustained release of the drug.

b) Non-effervescent Systems:

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These

systems may be referred to as the 'plug-type systems' since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Examples of this type of FDDS include colloidal gel barrier [24], microporous compartment system [25], alginate beads [26], and hollow microspheres [27].

Another type is a Fluid- filled floating chamber [28] which includes incorporation of a gas-filled floatation chamber into a microporous component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behaviour. The device is of swallowable size, remains afloat within the stomach for a prolonged time, and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated.

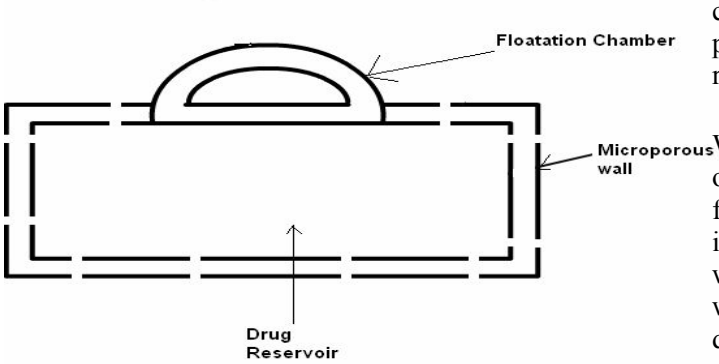

Fig.2. Gas filled floatation chamber

A newer Self-correcting floatable asymmetric configuration drug delivery system [29] has a 3-layer matrix to control the drug release. This 3-layer principle has been improved by development of an asymmetric configuration drug delivery system in order to modulate the release extent and achieve zero-order release kinetics by initially maintaining a constant area at the diffusing front with subsequent dissolution/erosion toward the completion of the release process. The system was designed in such a manner that it floated to prolong gastric residence time *in vivo*, resulting in longer total transit time within the gastrointestinal tract environment with maximum absorptive capacity and consequently greater bioavailability. This particular characteristic would be applicable to drugs that have pH-dependent solubility, a narrow window of absorption, and are absorbed by active transport from either the proximal or distal portion of the small intestine.

Yang *et al* [30] developed a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole, and clarithromycin) in Helicobacter pylori–associated peptic ulcers using HPMC and poly (ethylene oxide) (PEO) as the rate-controlling polymeric membrane excipients. The design of the delivery system was based on the swellable asymmetric triple-layer tablet approach. HPMC and poly(ethylene oxide) were the major rate-controlling polymeric excipients. Tetracycline and metronidazole were incorporated into the core layer of the triple-layer matrix for controlled delivery, while bismuth salt was included in one of the outer layers for instant release. The floatation was accomplished by incorporating a gas-generating layer consisting of sodium bicarbonate and calcium carbonate with swelleble polymers. Over 6-8 hours of sustained delivery of tetracycline and metronidazole was achieved with this dosage form which was still floating.

Streubel *et al* [31] prepared single-unit floating tablets based on polypropylene foam powder (Accurel MP 1000®) and matrix-forming polymer. Highly porous foam powder in matrix tablets provided density much lower than the density of the release medium. It was concluded that varying the ratios of matrix-forming polymers and the foam powder could alter the drug release patterns effectively.

Wu *et al* [32] prepared floating sustained release tablets of nimodipine by using HPMC and PEG 6000. Prior to formulation of floating tablets, nimodipine was incorporated into poloxamer-188 solid dispersion after which it was directly compressed into floating tablets. It was observed that by increasing the HPMC and decreasing the PEG 6000 content a decline in invitro release of nimodipine was observed.

Nur and Zhang [33] prepared floating tablets of captopril using HPMC (4000 and 15 000 cps) and carbopol 934P. It was concluded that the buoyancy of the tablet is governed by both the swelling of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids and the presence of internal voids in the centre of the tablet (porosity). A prolonged release from these floating tablets was observed as compared with the conventional tablets and a 24-hour controlled release from the dosage form of captopril was achieved.

Single-unit formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. The main drawback of such system is "all or none" phenomenon. In such cases there is a danger of passing of the dosage form to intestinal part

at the time of house-keeper waves. To overcome this difficulty multiple unit dosage forms are designed.

B. Multiple Unit Floating Systems:

In spite of extensive research and development in the area of HBS and other floating tablets, these systems suffer from an important drawback of high variability of gastrointestinal transit time, when orally administered, because of their all-or-nothing gastric emptying nature. In order to overcome the above problem, multiple unit floating systems were developed, which reduce the inter-subject variability in absorption and lower the probability of dose-dumping. Reports have been found on the development of both non-effervescent and effervescent multiple unit systems [34]. Much research has been focussed and the scientists are still exploring the field of hollow microspheres, capable of floating on the gastric fluid and having improved gastric retention properties.

a) Non-effervescent Systems:

No much report was found in the literature on non-effervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported [35]. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates and floats in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio.

b) Effervescent Systems (Gas-generating Systems):

Ikura *et al* [36] reported sustained release floating granules containing tetracycline hydrochloride. The granules are a mixture of drug granulates of two stages A and B, of which A contains 60 parts of HPMC, 40 parts of polyacrylic acid and 20 parts of drug and B contains 70 parts of sodium bicarbonate and 30 parts of tartaric acid. 60 parts by weight of granules of stage A and 30 parts by weight of granules of stage B are mixed along with a lubricant and filled into capsule. In dissolution media, the capsule shell dissolves and liberates the granules, which showed a floating time of more than 8 h and sustained drug release of 80% in about 6.5 h. Floating minicapsules of pepstatin having a diameter of 0.1-0.2 mm has been reported by Umezawa [37]. These minicapsules contain a central core and a coating. The central core consists of a granule composed of sodium bicarbonate, lactose and a binder, which is coated with HPMC. Pepstatin is coated on the top of the HPMC layer. The system floats because of the CO_2 release in gastric fluid and the pepstatin resides in the stomach for prolonged period. Alginates have received much attention in the development of multiple unit systems. Alginates are non-toxic, biodegradable linear copolymers composed of L-glucuronic and L-mannuronic acid residues. A multiple unit system prepared by Iannuccelli *et al* [38] comprises of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and concentration of PVA, resulted in enhancement of the floating properties of the system. Freeze-drying technique is also reported for the preparation of floating calcium alginate beads [39]. Sodium alginate solution is added drop wise into the aqueous solution of calcium chloride, causing the instant gelation of the droplet surface, due to the formation of calcium alginate. The obtained beads are freeze-dried resulting in a porous structure, which aid in floating. The authors studied the behaviour of radiolabeled floating beads and compared with nonfloating beads in human volunteers using gamma scintigraphy. Prolonged gastric residence time of more than 5.5 h was observed for floating beads. The nonfloating beads had a shorter residence time with a mean onset emptying time of 1 h.

Ichikawa *et al* [40] developed a new multiple type of floating dosage system having a pill in the core, composed of effervescent layers and swellable membrane layers coated on sustained release pills (shown in figure 3). The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sublayers to avoid direct contact between the 2 agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO_2 was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/ml.

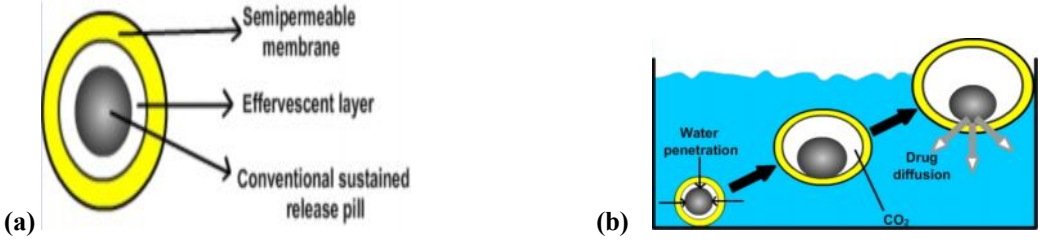

Fig.3 a) Different layers i) Semi-permeable membrane, ii) Effervescent Layer iii) Core pill layer b) Mechanism of floatation via CO_2 generation.

c) Hollow Microspheres:

Hollow microspheres are considered as one of the most promising buoyant systems , as they possess the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere. The general techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers such as polycarbonate, Eudragit® S and cellulose acetate were used in the preparation of hollow microspheres, and the drug release can be modulated by optimizing the polymer quantity and the polymer-plasticizer ratio.

Sustained release floating microspheres using polycarbonate were developed by Thanoo *et al* [41], employing solvent evaporation technique. Aspirin, griseofulvin and p-nitroaniline were used as model drugs. Dispersed phase containing polycarbonate solution in dichloromethane, and micronized drug, was added to the dispersion medium containing sodium chloride, polyvinyl alcohol and methanol. The dispersion was stirred for 3-4 h to assure the complete solvent evaporation, and the microspheres obtained were filtered, washed with cold water and dried. The spherical and hollow nature of the microspheres was confirmed by Scanning electron microscopic studies. The microspheres showed a drug payload of more than 50%, and the amount of drug incorporated is found to influence the particle size distribution and drug release. The larger proportion of bigger particles was seen at high drug loading, which can be attributed to the increased viscosity of the dispersed phase.

Kawashima *et al* [42] described hollow microspheres (microballoons) with drug in their outer polymer shells, prepared by a novel emulsion solvent diffusion method. A solution of drug and enteric acrylic polymer (Eudragit® S) in a mixture of ethanol and dichloromethane is added to the aqueous phase containing polyvinyl alcohol (0.75% w/v) and stirred continuously to obtain o/w emulsion. The microspheres obtained are filtered, water washed and dried. The diffusion and evaporation profiles of ethanol and dichloromethane, suggested a rapid diffusion of ethanol from the droplets into the aqueous phase, which might reduce the polymer solubility in the droplet because of insoluble property of Eudragit® S in dichloromethane. Hence, the polymer precipitation occurs instantly at the droplet surface, forming a film-like shell enclosing dichloromethane and drug. The microspheres showed good flow and packing properties, and a floating time of more than 12 h on acidic medium containing surfactant.

Joseph *et al* [28] developed a floating dosage form of piroxicam based on hollow polycarbonate microspheres. The microspheres were prepared by the solvent evaporation technique. Encapsulation efficiency of ~95% was achieved. *In vivo* studies were performed in healthy male albino rabbits. Pharmacokinetic analysis was derived from plasma concentration vs time plot and revealed that the bioavailability from the piroxicam microspheres alone was 1.4 times that of the free drug and 4.8 times that of a dosage form consisting of microspheres plus the loading dose and was capable of sustained delivery of the drug over a prolonged period

C. Raft Forming Systems:

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, wherein each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO_2. Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO_2 to make the system less dense and float on the gastric fluids[7]Jorgen *et al* [8,9] described an antacid raft forming floating system. The system contains a gel forming agent (e.g. alginic acid), sodium bicarbonate and acid neutralizer, which forms a foaming sodium alginate gel (raft) when in contact with gastric fluids. The raft thus formed floats on the gastric fluids and prevents the reflux of the gastric contents (i.e. gastric acid) into the esophagus by acting as a barrier between the stomach and esophagus. A patent assigned to Reckitt and Colman Products Ltd., describes a raft forming formulation for the treatment of helicobacter pylori (H. Pylori) infections in the GIT. The composition contained drug, alginic acid, sodium bicarbonate, calcium carbonate, mannitol and a sweetener. These ingredients were granulated, and citric acid was added to the granules. The formulation produces effervescence and aerates the raft formed, making it float.

Drugs Used In the Formulations of Stomach Specific Floating Dosage Forms

- *Floating microspheres* – Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen [43], Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol , Tranilast [44]and Terfinadine [45]
- *Floating granules* - Diclofenac sodium, Indomethacin and Prednisolone
- *Films* – Cinnarizine [46], Albendazole
- *Floating tablets and Pills* - Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin trihydrate, Atenolol, Fluorouracil, Isosorbide mononitrate [47], Para- aminobenzoic acid, Piretanide [48], Theophylline, Verapamil hydrochloride, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol[49], pentoxyfilline and Diltiazem HCl.

- *Floating Capsules* - Chlordiazepoxide hydrogen chloride, Diazepam [50], Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid [51] and Pepstatin, and Propranolol.

Polymers and other ingredients

Following types of ingredients can be incorporated into HBS dosage form in addition to the drugs:

- Hydrocolloids (20%-75%): They can be synthetics, anionic or non-ionic like hydrophilic gums, modified cellulose derivatives. Eg. Acacia, pectin, Chitosan,agar, casein, bentonite, veegum, HPMC(K4M, K100M and K15M),Gellan gum(Gelrite®), Sodium CMC, MC, HPC
- Inert fatty materials(5%-75%): Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. Eg. Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.
- Effervescent agents: Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine).
- Release rate accelerants(5%-60%): eg lactose, mannitol
- Release rate retardants (5%-60%): eg Dicalcium phosphate, talc, magnesium stearate
- Buoyancy increasing agents(upto80%): eg. ethyl cellulose
- Low density material: Polypropylene foam powder (Accurel MP 1000®).

Evaluation Parameters of Stomach Specific FDDS

Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting gastric residence *in vitro* floating behaviour show prolonged gastric residence *in vivo*.

However, it has to be pointed out that good *in vitro* floating behaviour 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.

1) Measurement of buoyancy capabilities of the FDDS [52]:

The floating behaviour was evaluated with resultant weight measurements. The experiment was carried out in two different media, deionised water and simulated meal, in order to monitor possible difference. The apparatus and its mechanism are explained earlier in this article. The results showed that higher molecular weight polymers with slower rate of hydration had enhanced floating behaviour and it was observed more in simulated meal medium compared to deionised water.

2) Floating time and dissolution:
The test for floating time measurement is usually performed in stimulated gastric fluid or 0.1 mole.lit^{-1} HCl maintained at 37^{0}C. It is determined by using USP dissolution apparatus containing 900 ml of 0.1 mole.lit^{-1} HCl as the dissolution medium at 37^{0}C. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time [53].
Recently Gohel *et al* [54] proposed a more relevant *in vitro* dissolution method to evaluate a floating drug delivery system (for tablet dosage form). A 100-mL glass beaker was modified by adding a side arm at the bottom of the beaker so that the beaker can hold 70 ml of 0.1 mole.lit^{-1} HCl dissolution medium and allow collection of samples. A burette was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 ml/min to mimic gastric acid secretion rate. The performance of the modified dissolution apparatus was compared with USP dissolution Apparatus 2 (Paddle). The problem of adherence of the tablet to the shaft of the paddle was observed with the USP dissolution apparatus. The tablet did not stick to the agitating device in the proposed dissolution method. The drug release followed zero-order kinetics in the proposed method. Similarity of dissolution curves was observed between the USP method and the proposed method at 10% difference level (f_2=57). The proposed test may show good *in vitro-in vivo* correlation since an attempt is made to mimic the *in vivo* conditions such as gastric volume, gastric emptying, and gastric acid secretion rate.

3) Drug release:
Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution.
4) Content uniformity, Hardness, Friability (Tablets)
5) Drug loading, drug entrapment efficiency, particle size analysis, surface characterization (for floating microspheres and beads):
Drug loading is assessed by crushing accurately weighed sample of beads or microspheres in a mortar and added to the appropriate dissolution medium which is then centrifuged, filtered and analyzed by various analytical methods like spectrophotometry. The percentage drug loading is calculated by dividing the amount of drug in the sample by the weight of

total beads or microspheres. The particle size and the size distribution of beads or microspheres is determined in the dry state using the optical microscopy method. The external and cross-sectional morphology (surface characterization) is done by scanning electron microscope (SEM) [55].

6) X-Ray/Gamma Scintigraphy:

X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form now a day [56]. It helps to locate dosage form in the g.i.t. and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a γ-emitting radio-nuclide in a formulation allows indirect external observation using a γ-camera or scintiscanner [57]. In case of γ-scintigraphy, the γ-rays emitted by the radio-nuclide are focused on a camera, which helps to monitor the location of the dosage form in the GI tract [58]

7) Pharmacokinetic studies:

Pharmacokinetic studies are the integral part of the *in vivo* studies and several works has been on that. Sawicki [59] studied the pharmacokinetics of verapamil, from the floating pellets containing drug, filled into a capsule, and compared with the conventional verapamil tablets of similar dose (40 mg). The t_{max} and AUC (0-infinity) values (3.75 h and 364.65 $ng.ml^{-1}h$ respectively) for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets. (t_{max} value 1.21 h, and AUC value 224.22 $ng.ml^{-1}h$). No much difference was found between the C_{max} values of both the formulations, suggesting the improved bioavailability of the floating pellets compared to the conventional tablets. An improvement in bioavailability has also been observed with piroxicam in hollow polycarbonate microspheres administered in rabbits. The microspheres showed about 1.4 times more bioavailability, and the elimination half-life was increased by about three times than the free drug.

Recent advances in stomach specific floating dosage forms

Ninan Ma *et al* [60] developed a type of multi-unit floating alginate (Alg) microspheres by the ionotropic gelation method with calcium carbonate ($CaCO_3$) being used as gas-forming agent. Attempts were made to enhance the drug encapsulation efficiency and delay the drug release by adding chitosan (Cs) into the gelation medium and by coating with Eudragit, respectively. The gastrointestinal transit of optimized floating sustained-release microspheres was compared with that of the non-floating system manufactured from identical material using the technique of gamma-scintigraphy in healthy human volunteers. It was found that the drug encapsulation efficiency of Cs–Alg microspheres was much higher than that of the Ca–Alg microspheres, and coating the microspheres with Eudragit RS could extend the drug release significantly. Both uncoating and coating microspheres were able to continuously float over the simulated gastric fluid (SGF) for 24 h *in vitro*. Prolonged gastricretention time (GRT) of over 5 h was achieved in the volunteer for the optimized coating floating microspheres (FM). In contrast, non-floating system (NFM) could be emptied within 2.5 h.

Strübing *et al* [61] investigated the mechanism of floating and drug release behaviour of poly (vinyl acetate)-based floating tablets with membrane controlled drug delivery. Propranolol HCl containing tablets with Kollidon® SR as an excipient for direct compression and different Kollicoat® SR 30 D/Kollicoat® IR coats varying from 10 to 20 mg polymer/cm^2 were investigated regarding drug release in 0.1 $mole.lit^{-1}$ HCl. Furthermore, the onset of floating, the floating duration and the floating strength of the device were determined. In addition, benchtop MRI studies of selected samples were performed. Coated tablets with 10 mg polymer/cm^2 SR/IR, 8.5:1.5 coat exhibited the shortest lag times prior to drug release and floating onset, the fastest increase in and highest maximum values of floating strength. The drug release was delayed efficiently within a time interval of 24 h by showing linear drug release characteristics.

Jang *et al* [62] has prepared a gastroretentive drug delivery system of DA-6034, a new synthetic flavonoid derivative, for the treatment of gastritis was developed by using effervescent floating matrix system (EFMS). The therapeutic limitations of DA-6034 caused by its low solubility in acidic conditions were overcome by using the EFMS, which was designed to cause tablets to float in gastric fluid and release the drug continuously. The release of DA-6034 from tablets in acidic media was significantly improved by using EFMS, which is attributed to the effect of the solubilizers and the alkalizing agent such as sodium bicarbonate used as gas generating agent. DA-6034 EFMS tablets showed enhanced gastroprotective effects in gastric ulcer-induced beagle dogs, indicating the therapeutic potential of EFMS tablets for the treatment of gastritis.

Sungthongjeen *et al* [63] have prepared a floating multi-layer coated tablets based on gas formation. The system consists of a drug-containing core tablet coated with a protective layer (hydroxypropyl methylcellulose), a gas forming layer (sodium bicarbonate) and a gas-entrapped membrane, respectively. Eudragit® RL 30D was chosen as a gas-entrapped membrane due to its high flexibility and high water permeability. The obtained tablets enabled to float due to the CO_2-gas formation and the gas entrapment by polymeric membrane. The effect of formulation variables on floating properties and drug release was investigated. The floating tablets using direct-compressed cores had shorter time to float and faster drug release than those using wet-granulated cores. The increased amount of a gas forming agent did not

affect time to float but increased the drug release from the floating tablets while increasing coating level of gas-entrapped membrane increased time to float (more then 8 hours) and slightly retarded but sustained drug release.

Rajnikanth and Mishra [64] have developed a floating in situ gelling system of clarithromycin (FIGC) using gellan as gelling polymer and calcium carbonate as floating agent for potentially treating gastric ulcers, associated with Helicobacter pylori. Gellan based FIGC was prepared by dissolving varying concentrations of gellan in deionized water to which varying concentrations of drug and sucralfate were dispersed well. The addition of sucralfate to the formulation significantly suppressed the degradation of clarithromycin at low pH. FIGC showed a significant anti-H. pylori effect than that of clarithromycin suspension. The in situ gel formulation with sucralfate cleared H.pylori more effectively than that of formulation without sucralfate. In addition, the required amount of clarithromycin for eradication of H. pylori was found to be less from FIGC than from the corresponding clarithromycin suspension. It was concluded that prolonged gastrointestinal residence time and enhanced clarithromycin stability resulting from the floating in situ gel of clarithromycin might contribute better for complete clearance of H. pylori.

Conclusion

The currently available polymer-mediated Non-effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be a very much effective approach to the modulation of controlled oral drug delivery. Number of commercial products and patents issued in this field are the evidence of it. The FDDS become an additional advantage for drugs that are absorbed primarily in the upper part of GI tract, i.e., the stomach, duodenum, and jejunum. Some of the unresolved, critical issues like the quantitative efficiency of floating delivery systems in the fasted and fed states, role of buoyancy in enhancing GRT of FDDS and more than that formulation of an ideal dosage form to be given locally to eradicate H.Pylori, responsible for gastric ulcers world wide. With an increasing understanding of polymer behaviour and the role of the biological factors mentioned above, it is suggested that future research work in the FDDS should be aimed at discovering means to control accurately the drug input rate into the GI tract for the optimization of the pharmacokinetic and toxicological profiles of medicinal agents. It seems that to formulate an efficient FDDS is sort of a challenge and the work will go on and on until an ideal approach with industrial applicability and feasibility arrives.

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