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Review Article

Future outlook hydrodynamic drug delivery system of solid oral dosage form: Review

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ABSTRACT

Over the last few years, therapeutic efficacy of drugs that have poor bioavailability or narrow absorption window have challenged the pharmaceutical industry. In this framework, many Hydrodynamic Balance System (HBS) also known as Gastro retentive dosage forms (GRDFs) have been used to enhance the therapeutic efficacy of drugs. Such drug have a narrow absorption window, are unstable at higher pH, are soluble in acidic conditions, and are local effect in the gastric-part. The drug development with recent technology of various novel polymeric-based gastroretentive drug delivery technologies that may regulate the bioavailability and extend time of therapeutic efficacy of such drugs. Our focus on the significance of in vitro study and in vivo evaluation parameters of various HBS drugs along with their applications. This study provides a promising platform for advantages and guide formulation of HBS dosage form were covered in detail.

1. Introduction

The oral route is by far the most preferred way of drug administration in the gastrointestinal tract due to ease of drug administration, high patient compliance, easy to handle, cost-effectiveness, for treating local gastrointestinal diseases and transport. While oral conventional drugs encounters difficulties such as limited bioavailability due to the heterogeneity of the gastrointestinal track (GIT), enzymatic activity, pH of the symbiotic flora, gastric retention time (GRT) of the drug.[1] All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (immediate, sustained, or controlled release) and the design of dosage forms (solid, dispersion, or liquid), must be developed within the intrinsic characteristics of GI physiology. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the GIT. For the successful development of an oral pharmaceutical drug delivery system consists of a basic understanding of the following three aspects.

1. Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug,
2. The anatomic and physiologic characteristics of the GIT and
3. Physicochemical characteristics and the drug delivery mode of the dosage form to be designed

Thus, the failure of conventional drug delivery systems to retain drugs in the stomach may lead to the development of HBS drug. However, the recent technological offer many benefits such as prolonged gastric residence time (PGRT) of dosage forms in the stomach up to extended time period, enhanced therapeutic efficacy by improving drug absorption, and rightness for targeted delivery in

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the GIT. Gastro-retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper GIT for local or systemic effects.[2] Floating systems or Hydro-dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and 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 the fluctuations in plasma drug concentration.[3] 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. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres.[4] Drug delivery systems are used for maximizing therapeutic index of the drug and reduction in side effects due to site-specific drug delivery. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

1.1. Situations where gastric retention is desirable

1. Drugs with narrow absorption windows in the upper small intestine, especially in the stomach. eg: Cyclosporin, Ciprofloxacin, Ranitidine
2. Drugs that have poor solubility in intestinal media
3. Drugs required for local action in stomach, Eg: Treatment of peptic ulcer
4. Drugs that degrade in colon and absorbed rapidly from G.I tract
5. Drugs those degrade in the colon.

1.2. Situations where gastric retention is not desirable

1. Drugs which are known to cause gastric lesions and slow release of such drugs in stomach are unwanted. eg: NSAIDS
2. Drugs that are rapidly degraded in its acidic environment
3. Drugs that are absorbed equally well throughout the G.I. tract,
4. Drugs that may irritate stomach lining

1.3. Requirements for gastric retention

Dosage form must be able to survive the forces caused by peristaltic waves in the abdominal and persistent contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. The device should be removed from the stomach with ease.

1.4. Approaches to gastric retention

Some methods have been tried in the preparation of gastro-retentive drug delivery systems. These include floating systems, swellable and expandable, high density systems, bioadhesive systems, altered shape systems, gel forming solution or suspension systems and sachet systems.[5,6]

Various approaches have been followed to encourage gastric retention of an oral dosage form.

1. Hydrodynamically balanced systems (HBS : incorporated buoyant materials enable the device to float;
2. **Effervescent systems:** gas-generating materials such as sodium bicarbonates or other carbonate salts are incorporated. These materials react with gastric acid and produce carbon dioxide, which entraps in the colloidal matrix and allows them to float.
3. **Low-density systems:** have a density lower than that of the gastric fluid so they are buoyant.
4. **Bioadhesive or mucoadhesive systems:** these systems permit a given drug delivery system (DDS) to be incorporated with bio/mucoadhesive agents, enabling the device to adhere to the stomach (or other GI) walls, thus resisting gastric emptying. However, the mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.
5. **High-density systems:** sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on diameter of the pellets.
6. **Large single- unit dosage forms:** these dosage forms are larger than the pyloric opening and so are retained in the stomach. There are some drawbacks associated with this approach. Permanent retention of rigid large-sized single- unit forms can cause bowel obstruction, intestinal adhesion and gastroplasty.
7. **Raft systems incorporate alginate gels:** these have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating of raft on gastric fluid.

1.5. Hydrodynamically Balanced System (HBS)

HBS is low-density systems that have enough buoyancy to float over the gastric fluid and persist floating in the stomach without affecting the gastric-emptying rate for an extended period of time. The drug is released gradually at the desired rate. This results in an increased GRT and an improved regulator of the fluctuations in plasma drug concentration. While, nominal gastric content required to allow the proper getting of the buoyancy retention principle, a minimal level of floating force (FF) is also required to retain the dosage form reliably buoyant on the surface of the meal. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres. Examples of various drugs formulated as different forms of FDDS.

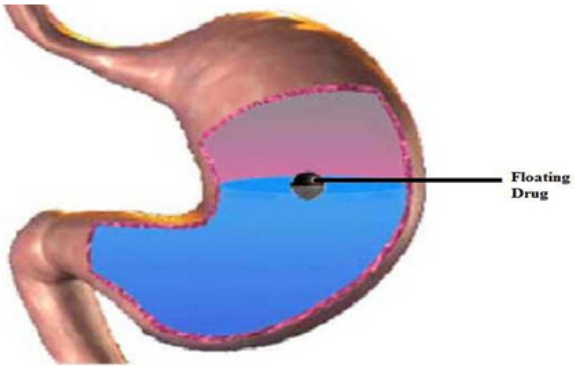

Fig. 1: Intragastric residence positions of floating unit.

The HBS is the novel dosage form, which when in interaction with gastric fluid and after dissolution of the outer exposed superficial of the dosage unit, forms a hydrated gel layer and maintains bulk density less than 1 g/cm^3. Thus, this system remains buoyant in the gastric fluid inside the stomach for more than 6 hrs. while conventional dosage forms break fully within 60 minutes and are emptied totally from the stomach just subsequently. This type of dosage form releases the drug through the hydrated layer by diffusion principle. The drugs, which are soluble at lower pH and have absorption window in the upper GIT. By varying the composition of the excipient between 22% and 72% w/w of one or more gel-forming hydrocolloids such as hydroxyethylcellulose, hydroxypropylcellulose, HPMC and sodium carboxymethylcellulose, the granules into compressed into tablets or encapsulated into capsules, which results in the desired release rate of the drug. This hydrated gel controls the rate of solvent penetration into the device and the rate of drug release from the device.

1.6. Classification of floating drug delivery

Floating drug delivery systems are classified depending on the use of two formulation variables: effervescent and non-effervescent systems.

1. **Effervescent Floating Dosage Forms:** These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, $C0_2$ is liberated and gas entrapped in swollen hydrocolloids which provides buoyancy to the dosage forms.

   (a) **Volatile liquid containing system:** The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of Poly vinyl alcohol, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

   (b) **Gas-generating Systems:** These buoyant delivery systems utilize effervescent reactions between carbo- ante/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme.

2. **Non-effervescent Floating Dosage Forms:** Non-effervescent floating dosage forms use a gel forming or swellable cellulose type hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass. The various types of this system are as:

   (a) **Single Layer Floating Tablets :** They are formulated by intimate mixing of drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains bulk density of less than unity. They are formulated by intimate mixing of drug with low-density enteric materials such as HPMC.

(b) **Bi-layer Floating Tablets :** A bi-layer tablet contain two layer one immediate release layer which releases initial dose from system while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gel barrier on its surface, and maintain a bulk density of less than unity and thereby it remains buoyant in the stomach.

(c) **Alginate Beads :** Multi-unit floating dosage forms were developed from freeze dried calcium alginate. Spherical beads of approx. 2.5 mm diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing precipitation of calcium alginate leading to formation of porous system, which can maintain a floating force for over 12 hours. When compared with solid beads, which gave a short residence time of 1 hour, and these floating beads gave a prolonged residence time of more than 5.5 hours.

(d) **Hollow Microspheres :** Hollow microspheres (microballoons), loaded with drug in their outer polymer shells are prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer is poured into anagitated aqueous solution of PVA that is thermally controlled at 40 °C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane forms an internal cavity in microsphere of polymer with drug. The microballoons float continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours.[7]

1.7. Drug Candidates Suitable For FDDS

1. Drugs that have narrow absorption window in GIT (e g L-DOPA, paminobenzoic acid, furosemide, riboflavin.
2. Drugs those are locally active in the stomach (e g misroprostol, antacids.
3. Drugs those are unstable in the intestinal or colonic environment (e.g. captopril, ranitidine HCl, metronidazole).
4. Drugs that disturb normal colonic microbes (e.g. antibiotics used for the eradication of Helicobacter pylori, such as tetracycline, clarithromycin,amoxicillin).
5. Drugs that exhibit low solubility at high pH values (e g diazepam, chlordiazepoxide, verapamil.

1.8. Mechanism of Floating Systems

Various attempts have been made to retain the dosage form in the GI track as a way of swelling 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. 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 lowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. His results in an increased GRT and a better control of his fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the roper 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. 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.[8–12]

F = F buoyancy - F gravity

= (Df - Ds) gv— (1)

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

Ds = object density, v = volume and g = acceleration due to gravity.

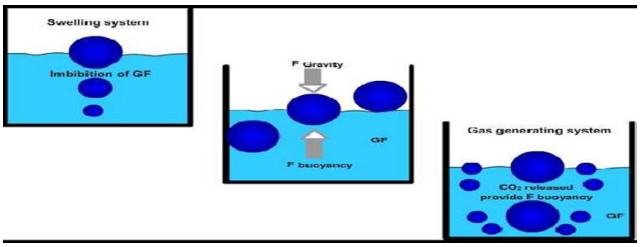

Fig. 2: Various floating dosage forms action

1.9. Advantages of floating drug delivery system

1. Improves patient compliance by decreasing dosing frequency.
2. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
3. Better therapeutic effect of short half-life drugs can be achieved.

4. Gastric retention time is increased because of buoyancy.
5. Drug releases in controlled manner for prolonged period.

1.10. Applications of floating drug delivery system

1. Sustained Drug Delivery
2. Site-Specific Drug Delivery
3. Absorption Enhancement

1.11. Factors affecting floating drug delivery system

1. Density: Density of the dosage form should be less than the gastric contents (1 004gm/ml
2. **Size and Shape :** Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kiloponds per square inch are reported to have better GIT for 90 to 100 % retention at 24 hours compared with other shapes.
3. **Fed or Unfed State :** Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short.
4. **Nature of the meal :** Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release.
5. **Caloric Content :** GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats.
6. **Frequency of feed :** The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
7. **Gender :** Mean ambulatory GRT in meals (3.4±0.4 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.
8. Age: Elderly people, especially those over 70 years have a significantly longer GRT
9. Posture: GRT can vary between supine and upright ambulatory states of the patients
10. **Concomitant drug administration :** Anticholinergic like atropine and propentheline opiates like codeine and prokinetic agents like metoclopramide.
11. **Biological factors:** Diseases like gastroenteritis, gastric ulcer, pyloric stenosis, The Pharma Research Diabetes and hypothyroidism retard gastric emptying. Partial or total gastrectomy, duodenal ulcer and hypothyroidism promote gastric emptying rate.

1.12. Approaches To Design Floating Dosage Forms:

1. Low density of GRDF that cause buoyancy above gastric fluid
2. High density which retain the dosage form in the body of stomach
3. Concomitant administration of drugs or excipients which slow the motility of GIT
4. Bio adhesive
5. Swelling to a large size which prevents emptying of dosage form through the pyloric sphincter.

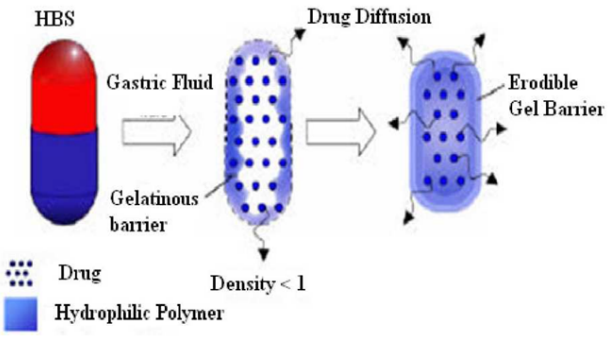

Fig. 3: Mode of drug release from HBS capsule

1.13. Evaluation of floating dosage forms

1. **Floating lag time:** It is the time taken by the tablet to emerge onto the surface of dissolution medium and is expressed in seconds or minutes.
2. **In vitro drug release and duration of floating**: This is determined by using USP II apparatus (paddle) stirring at a speed of 50 or 100 rpm at 37 ± 0.2 °c in simulated gastric fluid (pH 1.2 without pepsin). Aliquots of the samples are collected and analyzed for the drug content. The time (hrs) for which the tablets remain buoyant on the surface of the dissolution medium is the duration of floating and is visually observed.
3. **In vivo evaluation for gastro-retention:** This is carried out by means of X- ray or Gamma scintigraphic monitoring of the dosage form transition in the GIT. The tablets are also evaluated for hardness, weight variation, etc. [13–15]

1.14. Drugs Used as Gastro retentive Dosage Form

2. Conclusion

HBS have unlimited possible to expand the therapeutic efficacy of drugs with high solubility at acidic pH, narrow-

Table 1: List of drugs formulated as single and multiple unit forms of FDDS

Tablets	Cholrpheniramine maleate, Theophylline, Furosemide, Ciprofloxacin, Captopril, Acetylsalicylic acid, Nimodipine, Amoxycillin trihydrate, Verapamil HCI, Isosorbide dinitrate, Sotalol, Isosorbide mononitrate, Aceraminophen, Ampicillin, Cinnarazine, Dilitiazem, Florouracil, Piretanide, Prednisolone, Riboflavin-5'Phosphate.
Capsules	Nicardipine, L-Dopa and benserazide, chlordizepoxide HCI, Furosemide, Misoprostal, Diazepam, Propranlol, Urodeoxycholic acid.
Microspheres	Verapamil, Aspirin, Griseofulvin, and p-nitroanilline, Ketoprofen, Tranilast, Iboprufen, Terfenadine
Granules	Indomethacin, Diclofenac sodium, Prednisolone.

absorption windows and instability at alkaline pH. A systematic indulgent of the anatomy and physiological state of the GI track, studies into the impact of formulation, process and method variables on dosage form quality is a precondition for the successful design of HBS dosage. As from the pharmaceutical part, upcoming ways of HBS dosage may essential to emphasis on a combination approach of GRDDS to attain better and efficient product quality. Besides, a scientific approach could be used to better recognize the effects of formulation and process variable on product quality and performance.

3. Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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None.

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