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THE RECENT DEVELOPMENTS ON GASTRIC FLOATING DRUG DELIVERY SYSTEMS: AN OVERVEIW

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ABSTRACT: The purpose of this review on Floating Drug Delivery Systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables which affect the gastric retention and approaches to design single-unit and multiple unit floating systems, their classification and formulation aspects are covered in detail. This review also summarizes various sophisticated and modern *in-vitro* techniques to evaluate the performance, advantages and applications of floating systems. These systems are useful to avoid all the problems that are encountered during the development of a pharmaceutical dosage forms. Thus floating drug delivery systems seems to be the promising delivery systems for control release of drugs.
Key words: Floating Drug Delivery Systems, *in-vitro,* hydro dynamically balanced systems.

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. One of such difficulties is the ability to confine the dosage form in the desired area of the gastrointestinal tract[1].To over come this physiological problem, several drug delivery systems with prolonged gastric retention time have been investigated[2,3,4].Attempts are being made to develop a controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer durations, there by reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady state by delivering drug in a controlled and reproducible manner[5].

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 of drugs that are less soluble in high pH environment. Gastric retention to provide new therapeutic possibilities and substantial benefits form patients.

The controlled gastric retention of solid dosage forms may be achieved by the mechanism of mucoadhesion,[6,7] floatation,[8] sedimentation,[9,10] expansion,[11,12] modified shape systems[13,14] or by the administration of pharmacological agents [15,16] that delaying gastric emptying. Based on these approaches, floating drug delivery systems seems to be the promising delivery systems for control release of drugs.

FLOATING DRUG DELIVERY SYSTEMS:

Floating systems or dynamically controlled systems are low-density systems that have sufficiently buoyancy to float over the gastric contents and remain buoyant in the stomach with out affecting the gastric emptying rate for a prolonged period of time.(fig:3) This results in an increased gastric retention time and a better control of the fluctuations in plasma drug concentration. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hallow Microspheres.

BASIC GIT PHYSIOLOGY:

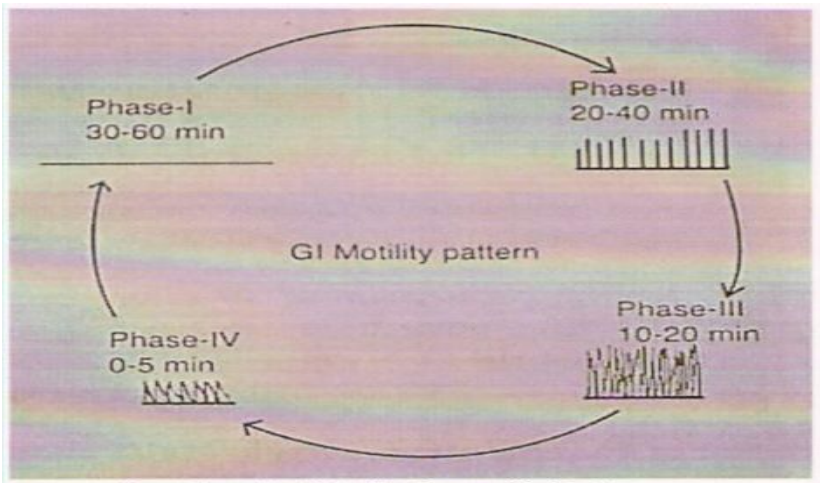
Anatomically the stomach is divided in to three regions:

Fundus, Body and Antrum (pylorus).The proximal part made of fundus and body acts as a reservoir for undigested materials, where as the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions.[17]

Gastric emptying occurs in both the fasting and fed states. During the fasting state an interdigestive series of electrical events take place which cycle both through stomach and intestine every 2-3 hrs[18] which is called as interdigestive myloelectric cycle or migrating myloelectric cycle (MMC) which is further divided in to four phases After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state which is also termed as digestive motility pattern. (Fig2).

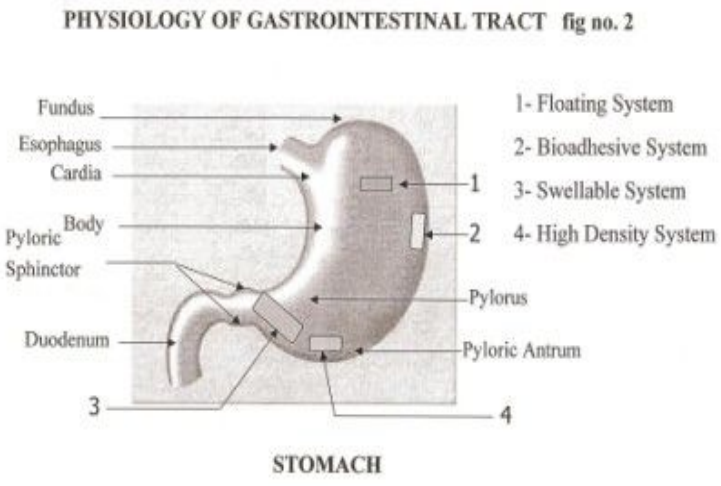
1. Phase 1-(Basic phase)-last from 30-60 minutes with rare contractions.
2. Phase 2-(Preburst phase)-last for 20-40 minutes with intermittent action potential and contractions.
3. Phase 3-(Burst phase)- last for 10-20 minutes which includes intense and regular contractions for short period.
4. Phase 4-last for 0-5 minutes and occurs between phase 2 and 1of 2 consecutive cycles (Fig1).

Fig1:



Gastro intestinal Motility Pattern Fig.No.1

Fig2:



After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state which is also termed as digestive motility pattern.

FACTORS INFLUENCING GASTRIC RETENTION:

Gastric residence time of an oral dosage form is influenced by many factors. To pass through the pyloric size should be in the range of 1-2 mm[19].The pH of the stomach in fasting state and fed state are 1.5-2.0 and 2.0-6.0 respectively. A large volume of waste administrated in oral dosage form raises the pH of the stomach contents to 6-9.The rate of gastric emptying depends mainly on viscosity, volume and caloric contents of meals .It does not make any difference whether the meal has high protein, fat or carbohydrate contents as long as the caloric content is the same while there is decrease in gastric emptying time by increasing acidity and caloric value.

Other factors influences such as biological factors which includes age, body mass, index, gender, posture and diseased states (Hepatic failure, Diabetes, Chrons' disease). In case of elderly persons gastric emptying is slowed down. Females have slower gastric emptying rates than that of males. Stress increases the gastric emptying rates where as depression slows it down. Volume of liquids administered also effects the gastric emptying time. Larger the liquid content, faster the emptying.

Several formulations parameters can effect the gastric residence time such as Size, Shape, Density, Diameter etc, of the dosage unit which affects gastric emptying.[20] Out of all ring shaped devices have better gastric rates when compared to all other shapes. Formulations having a diameter more than 7.5mm shows better gastric residence time compared with formulations having 9.9mm. Density of a dosage form influences the gastric emptying rate. A buoyant dosage form having a density of less than that of the gastric fluids. So the unit is retained in the stomach for a prolonged period.

Out of all the floating drug delivery system formulations are having reliable gastric emptying patterns due to free distribution of the drug through out the GIT when compare to single unit formulations.

APPROACHES TO DESIGN FLOATING DOSAGE FORMS:

The following approaches have been used for the design of floating dosage forms of single and multiple unit systems. [22]

SINGLE –UNIT DOSAGE FORMS:

In low density approaches [23] the globular shells apparently having lower density than that of gastric fluid can be used as a carriers like popcorn, poprice, polystrol for the drug for its controlled release. The polymer of choice can be either Ethyl cellulose or HPMC. Depending on type of release desired. Finally the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration. Fluid filled floating chamber [24] type of dosage forms includes incorporation of a gas filled floatation chamber in to a micro porous component that houses as a reservoir having apertures present at top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug.

I) HYDRO DYNAMICALLY BALANCED SYSTEMS (HBS):

These systems are designed to prolong the stay of the dosage forms in the gastric intestinal tract and aid in enhancing the absorption. Drugs having a better solubility in acidic environment and also having specific site of absorption in the upper part of small intestine is achieved by these HBS systems. To retain in stomach for a prolonged period of time the dosage form must have bulk density of less than '1' and has to maintain its structural integrity and release drug constantly from the dosage form. Among all the advantages single-unit formulations are associated with some limitations/problems such as sticking together or being obstructed in the GIT which may lead to potential danger of producing irritation.

MULTIPLE-UNIT DOSAGE FORMS:[25]

Multiparticulate dosage forms are gaining much favor over single-unit dosage forms.[34] The potential benefits include increased bioavailability; predictable, reproducible and generally short gastric residence time, no risk of dose dumping; reduced risk of local irritation, and the flexibility to blend pellets with different compositions or release patterns. Because of their smaller particle size these systems are capable of passing through the GI tract easily, leading to less inter- and intra-subject variability. However, potential drug loading of a multiparticulate system is lower because of the proportionally higher need for excipients (e.g., sugar cores). Most multiparticulate Pulsatile delivery systems are reservoir devices coated with a rupturable polymeric layer. Upon water ingress, drug is released from the core after rupturing of the surrounding polymer layer, due to pressure build-up within the system. The pressure necessary to rupture the coating can be achieved with swelling agents, gas-producing effervescent excipients or increased osmotic pressure. Water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time. Water soluble drugs are mainly released by

diffusion; while for water insoluble drug, the release is dependent on dissolution of drug.

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS:

Floating drug delivery systems are classified depending up on the two formulations variables Effervescent and Non-effervescent systems.

EFFERVESCENT FLOATING DOSAGE FORMS:

These are the matrix types of systems which are prepared by using swellable like methylcellulose, HPMC and chitosan based polymers as well as various effervescent compounds like sodium carbonate, calcium carbonate, tartaric acid and citric acid .They are formulated in such a way that when in contact with the acidic gastric contents liberation of CO_2 takes place and gets entrapped in to the swollen hydrocolloids which provides buoyancy to the dosage forms such as Famotidine, [82] Amlodipine besylate.[83]

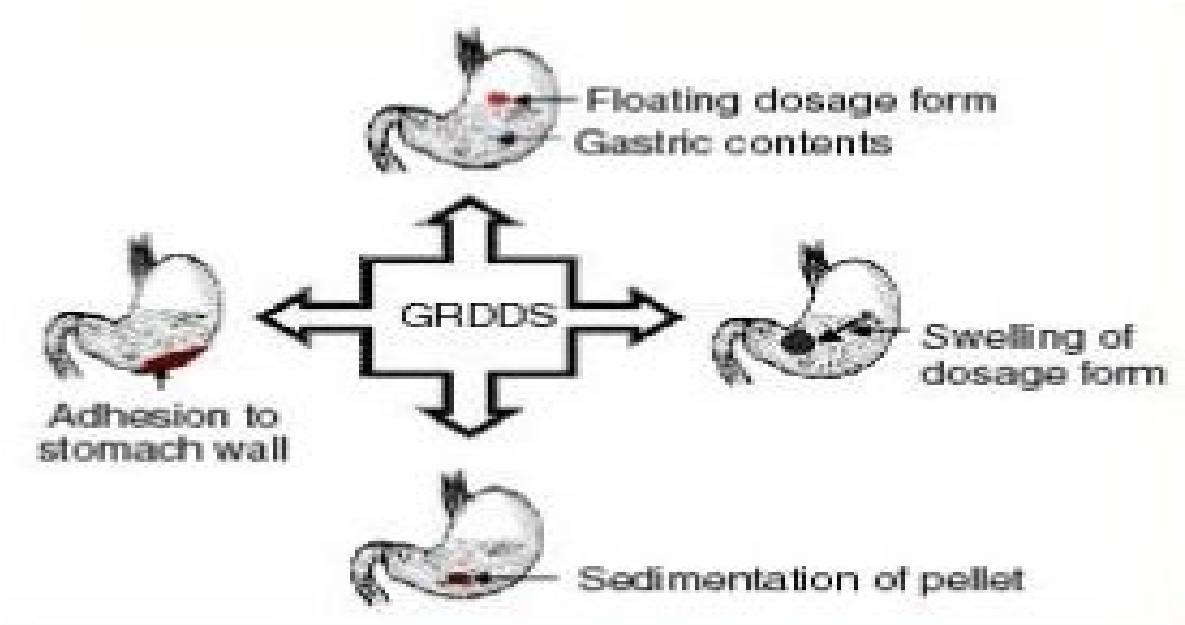
NON-EFFERVESCENT FLOATING DOSAGE FORMS:

These dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides and matrix forming polymers like polycarbonates, polymethaacrylate and polystyrene. The formulation is done by mixing the drug and the gel-forming hydrocolloid after oral administration of this dosage form swells while in contact with gastric fluids attains bulk density of <1.The buoyancy of dosage form was attained due to the air entrapment in to the swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass. Drugs such as Famotidine[84], levodopa.[85]

EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS:

Various parameters that need to be evaluated in gastro retentive formulations which includes floating duration, dissolution profiles, specific gravity, content uniformity, hardness and friability in case of solid dosage forms. In case of multiparticulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, mechanical properties and x-ray diffraction studies are performed.

Fig: 3



CHARACTERIZATION PARAMETERS:

SIZE AND SHAPE EVALUATION: [27, 76]

The particle size and shape plays a major role in determining solubility rate of the drugs and thus potentially its bioavailability[76]**.** The particle size of the formulation was determined using Sieve analysis, Air elutriation (Bahco^{TM}) analysis, Photoanalysis, Optical counting method, microscope, Electroresistance counting methods (Coulter counter), Sedimentation techniques, Laser diffraction methods, ultrasound attenuation spectroscopy , Air Pollution Emissions Measurements etc.[86]

FLOATING PROPERTIES: [87]

Effect of formulation variables on the floating properties of gastric floating drug delivery system was determined by using continuous floating monitoring system and statistical experimental design.

SURFACE TOPOGRAPHY: [27, 77]

The surface topography and structures were determined using scanning electron microscope (SEM) operated with an acceleration voltage of 10k.v, Contact angle meter, Atomic force microscopy (AFM), Contact profiliometer.

DETERMINATION OF MOISTURE CONTENT: [28, 78]

The water content per se is seldom of interest. Rather, it shows whether a product intended for trade and production has standard properties such as

- Storability
- Agglomeration in the case of powders
- Microbiolgical stability
- Flow properties, viscosity
- Dry substance content
- Concentration or purity
- Commercial grade (compliance with quality agreements)

Thus moisture content of the prepared formulations was determined by Karl fisher titration, vacuum drying, Thermo gravimetric methods, Air oven method, Moisture Meters, Freeze drying as well as by physical methods.

SWELLING STUDIES: [28, 79]

Swelling studies were performed to calculate molecular parameters of swollen polymers [79]**.** Swelling studies was determined by using Dissolution apparatus, optical microscopy and other sophisticated techniques which include H^1NMRimaging, Confocal laser scanning microscopy (CLSM), Cryogenic scanning electron microscopy (Cryo-SEM), Light scattering imaging (LSI) etc.

The swelling studies by using Dissolution apparatus was calculated as per the following formula.

$$\text{Swelling ratio} = \frac{\text{Weight of wet formulations}}{\text{Weight of formulations}}$$

DETERMINATION OF THE DRUG CONTENT: [29, 88]

Percentage drug content provides how much amount of the drug that was present in the formulation. It should not exceeds the limits acquired by the standard monographs.Drug content was determined by using HPLC,HPTLC methods, Near infrared spectroscopy (NIRS) ,Microtitrimetric methods, Inductively Coupled Plasma Atomic Emission Spectrometer (ICP-AES) and also by using spectroscopy techniques.

PERCENTAGE ENTRAPMENT EFFICIENCY: [29]

Percentage entrappment efficiency was reliable for quantifying the phase distribution of drug in the prepared formulations.Entrapment efficiency was determined by using three methods such as Microdialysis method, Ultra centrifugation, and pressure Ultra filtration.

IN-VITRO RELEASE STUDIES: [89, 90]

In vitro release studies were performed to provide the amount of the drug that is released at a definite time period. Release studies were performed by using Franz diffusion cell system and synthetic membrane as well as different types of dissolution apparatus.

POWDER X-RAY DIFFRACTION: [77, 81]

X-ray powder diffraction is the predominant tool for the study of polycrystalline materials and is eminently suited for the routine characterization of pharmaceutical solids. Samples were irradiated with α radiation and analyzed between 2 ºC and 60 ºC .The voltage and current used were 30KV and 30mA respectively.

FOURIER TRANSFORM INFRARED ANALYSIS (FT-IR): [28, 77]

Fourier transform infrared spectroscopy (FT-IR**)** is a technique mostly used to identify organic, polymeric, and some inorganic materials as well as for functional group determination. Fourier Transform Infrared Analysis (FT-IR) measurements of pure drug, polymer and drug-loaded polymer formulations were obtained on FT-IR. The pellets were prepared on KBr-press under hydraulic pressure of 150kg/cm^2; the spectra were scanned over the wave number range of 3600 to 400 cm^{-1} at the ambient temperature.

DIFFERENTIAL SCANNING CALORIMETRY (DSC): [31, 80]

DSC is used to characterize water of hydration of pharmaceuticals .Thermo grams of formulated preparations were obtained using DSC instrument equipped with an intracooler.Indiun/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample preparations were hermitically sealed in an aluminium pan and heated at a constant rate of 10ºC/min; over a temperature range of 25º C - 65º C .Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50ml/min.

ADVANTAGES OF FDDS:[32, 33]

- Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.
- FDDS are advantageous for drugs meant for local action in the stomach eg:Antacids
- FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhea to keep the d5ug in floating condition in stomach to get a relatively better response.
- Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.
- The FDDS are advantageous for drugs absorbed through the stomach eg: Ferrous salts, Antacids.

List of drugs explored for various floating dosage forms:

Microspheres Tablets /Pills	**Granules**
Chlorpheniramine maleate [35]	*Cinnarizine*[52]
Aspirin, [35] *griseofulvin*[35]	*Diclofenac sodium* [53]
Acetaminophen [36, 37]	*Diltiazem* [54]
p-nitroaniline [38]	*Indomethacin* [55]
Acetylsalicylic acid [39]	*Fluorouracil* [56]
Ibuprofen[40]	*Prednisolone* [57]
Amoxycillin trihydrate [41]	*Isosorbide mononitrate* [51]
Terfenadine [42]	*Isosorbide dinitrate* [49]
Ampicillin [43]	**Powders**
Tranilast[40, 44]	*Riboflavin-59-phosphate* [62,63]
Atenolol [45, 46]	*Sotalol* [50]
Theophylline[47]	*Theophylline* [47]
Captopril[48]	**Capsules**
Isosorbide di nitrate[49]	
Sotalol[50]	*Verapamil HCl* [64,65,66]
Isosorbidemononitrate[51]	*Chlordiazepoxide HCl* [67]
Films	*Diazepam 67,68*
p-*Aminobenzoic acid* [58,59]	*Furosemide* [69]
Cinnarizine[52]	*L-Dopa and benserazide* [70]
Piretanide [60]	*Misoprostol* [71,72]
Prednisolone[57]	*Propranolol HCl* [73]
Quinidine gluconate [61]	*Ursodeoxycholic acid* [74]
	Nicardipine[75]

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS:

ENHANCED BIOAVAILABILITY:

The bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption.

SUSTAINED DRUG DELIVERY:

Oral CR formulations are encountered with problems such as gastric residence time in the GIT. These problems can be overcome with the HBS systems which can remain in the stomach for long periods and have a bulk density <1 as a result of which they can float on the gastric contents. These systems are relatively larger in size and passing from the pyloric opening is prohibited.

SITE –SPECIFIC DRUG DELIVERY SYSTEMS:

These systems are particularly advantageous for drugs that are specifically absorbed from the stomach or the proximal part of the small intestine .The controlled, slow delivery of

drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency. eg: Furosemide and Riboflavin.

ABSORPTION ENHANCEMENT:

Drugs which are having poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption.

MINIMIZED ADVERSE ACTIVITY AT THE COLON:

Retention of the drug in the HBS systems at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

REDUCED FLUCTUATIONS OF DRUG CONCENTRATION:

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index

CONCLUSION:

Gastro-retentive floating drug delivery systems have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs .The increasing sophistication pf delivery technology will ensure the development of increase number of gastric retentive drug delivery to optimize the delivery of molecules that exhibits absorption window, low bioavailability of extensive first pass metabolism.

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