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An overview on various approaches to Gastroretentive dosage forms

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Abstract

Over the past four decades, gastro retentive dosage forms have recently become a leading methodology in the field of site-specific orally administered controlled release drug delivery system.. Gastroretentive dosage forms have the potential to improve local therapy with an increase of short gastric residence time and unpredictable gastric emptying time and decrease the variation in bioavailability which is unobserved, in other commercially available preparations. With the advent to current scientific and patented literature, this review have covered in detail the recent developments of FDDS including the physiological and formulation variables affecting gastric retention, classification, approaches to design single and multiple unit floating systems, formulation aspects and invitro and invivo studies to evaluate the performance.

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INTRODUCTION

Even though various drug delivery systems are used for maximizing therapeutic index and reduction in the side effects of the drug, oral route remains the preferred, promising and effective route for the administration of therapeutic agents. Because, low cost of therapy, ease of administration, flexibility in formulation and handling leads to higher level of

patient compliance. Approximately 50% of the drug delivery systems available in the market are oral drug delivery system [1].

Although tremendous advances seen in de novo design of an oral controlled drug delivery system during last two decades, it has limited success in case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). This approach is bedilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose [2].

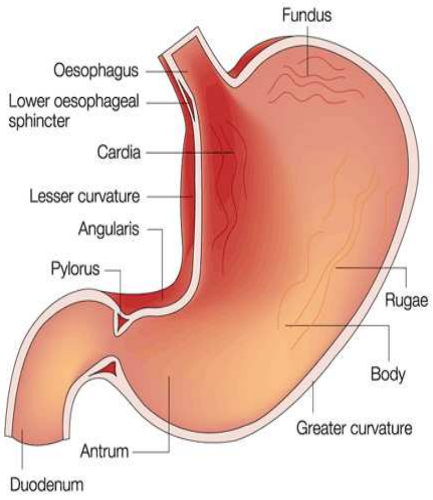
To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolonged gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment [3].

Several gastro retentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach [4], low density (floating) systems that causes buoyancy in gastric fluid [5, 6, 7], mucoadhesive systems that causes bioadhesion to stomach mucosa [8], unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach [9,10], superporous hydrogel systems[11], magnetic systems [12] etc. .

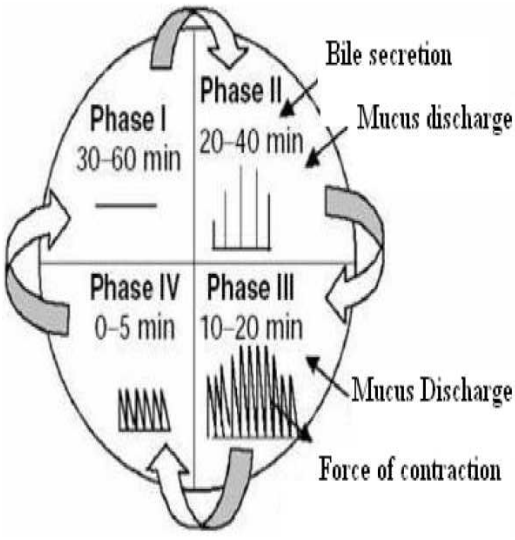
BASIC GIT PHYSIOLOGY

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 materials, where as the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions [13,14]. 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, 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 [15].



Structure of stomach



Schematic representation of interdigestive motility

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 1 of 2 consecutive cycles.

ADVANTAGES OF FDDS

1. Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine
2. FDDS are advantageous for drugs meant for local action in the stomach eg: Antacids.
3. FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhea to keep the drug in floating condition in stomach to get a relatively better response.
4. 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.
5. The FDDS are advantageous for drugs absorbed through the stomach eg: Ferrous salts, Antacids [13,14,15].

DISADVANTAGES OF FDDS

1) Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.
2) Drugs such as Nifedipine, which is well absorbed along the entire GI tract and which undergo significant first pass metabolism, may not be suitable candidates for FDDS.
3) One of the disadvantages of floating systems is that they require a sufficiently high level of fluids in the stomach, so that the drug dosage form float therein and work efficiently.
4) These systems also require the presence of food to delay their gastric emptying [16,17].

POTENTIAL DRUG CANDIDATES FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

1) Drugs those are locally active in the stomach e.g misoprostol, antacids etc.
2) Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-DOPA, para aminobenzoic acid, furosemide, riboflavin etc.
3) Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl,
4) Drugs that disturb normal colonic microbes e.g.antibiotics against Helicobacter pylori.
5) Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.

DRUGS THOSE ARE UNSUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

1) Drugs that have very limited acid solubility e.g. phenytoin etc.
2) Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
3) Drugs intended for selective release in the colon. eg. 5- amino salicylic acid and corticosteroids etc.[18].

POLYMERS AND OTHER INGREDIENTS USED FOR THE PREPARATIONS OF FLOATING DRUGS

i) Polymers: The following polymers used to preparations of floating drugs: HPMC K4 M, Calcium alginate, Eudragit S100 Eudragit RL, Propylene foam, Eudragit RS, ethyl cellulose, poly methyl methacrylate, Methocel K4M, Polyethylene

oxide, β Cyclodextrin, HPMC 4000, HPMC 100, CMC, Polyethylene glycol, polycarbonate, PVA, Polycarbonate, Sodium alginate, HPC-L, HPC, Eudragit S, HPMC, Metolose S.M. 100, PVP, HPC-H, HPC-M, HPMC K15, Polyox, HPMC K4, Acrylic polymer E4 M and Carbopol [13,14,15].

ii) **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. E.g. Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.

iii) **Effervescent agents:** Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine).

iv) **Release rate accelerants (5 - 60%):** eg. lactose, mannitol.

v) **Release rate retardants (5 - 60%):** eg. Dicalcium phosphate, talc, magnesium stearate

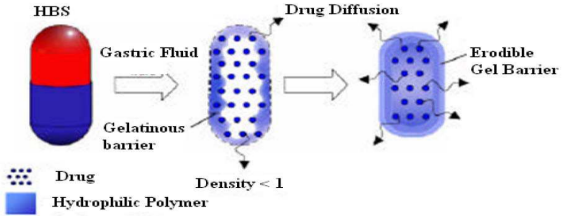
vi) **Buoyancy increasing agents (upto 80%):** eg. Ethyl cellulose

vii) **Low density material:** Polypropylene foam powder (Accurel MP 1000®).

Approaches to GRDDS

To formulate a successful stomach specific or gastroretentive drug several techniques are currently used such as

a) Hydrodynamically balanced systems (HBS): The incorporated buoyant materials enable the device to float. [19,20]. The gelatinous polymer barrier formation result from hydrophilic polymer swelling. Drug is released by diffusion and erosion of the gel barrier**.**



Hydrodynamically balanced systems (HBS)

b) ***Raft systems incorporating alginate gels***: These have a carbonate component and, upon reaction with gastric acid, bubbles form in the gel, enabling floating [21,22].

c) ***Bioadhesive or Mucoadhesive systems*** These systems are used to localize a delivery device within the lumen and cavity of the body to increase the drug absorption process in a site-specific manner. In these approaches involve the use of bioadhesive polymers are used that can be adhered to the epithelial surface of the GIT [20].

d) Modified shape systems- These are non-disintegrating geometric shapes molded from silastic elastomer or exuded from polyethylene blends and extend the gastric transit time (GTT) depending on the size, shape and flexural modulus of the drug delivery device [21].

e) ***High density systems –*** They include coated pellets and have density greater than that of stomach content (1.004 gm/cm). This goal is achieved by coating the drug with a heavy inert material such as barium sulphate, ZnO, titanium dioxide. This formulation of high density pellet is based on assumption that heavy pellets might remain longer in the stomach, since they are positioned in the lower part of the antrum [23, 24].

f) ***Swelling system***- These types of products swell to an extent that prevents their exit from the stomach through the pylorus. This dosage form retained in the stomach for a longer period of time. These systems may be referred as a "Plug type system," since they exhibit tendency to remain logged in the pyloric sphincters [25-27].

g)***Magnetic systems***- These are the systems which includes external stimuli as magnetic field for site specific delivery. Some magnetically active compounds can be incorporated in the dosage form to achieve site specificity [25-27].

h)***Floating drug delivery system*** Floating systems, first described by Davis in 1968, have bulk density lower than that of the gastric fluid and thus remain buoyant in stomach for a prolong period. Swelling delivery systems are capable of swelling to a

size that prevents their passage through the pylorus. Upon coming in contact with gastric fluid, the polymer imbibes water and swells; as a result the dosage form is retained in the stomach for a longer period of time [28, 29].

Floating drug delivery systems

Non-effervescent system : This type of system, after swallowing, swells via imbibitions of gastric fluid to an extent that prevents their exit from the stomach. The formulation methods of such type dosage form involves the mixing of the drug with a gel, which swells when comes in contact with gastric fluid and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier [30]. The air trapped by the swollen polymer provides buoyancy to these dosage forms. This system can be further divided into four sub-types

***(i) Colloidal gel barrier system*:** Sheth and Tossounian first designated this ' hydrodynamically balanced system [31]. These type of systems contain drug with gel forming hydrocolloids which allow them to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug at its absorption site in the solution form for ready absorption. This system incorporates a high level of one or more gel forming highly soluble cellulose type hydrocolloid as hydroxypropyl cellulose, hydoxy ethyl cellulose, hydroxyl propylmethylcellulose (HPMC), polysaccharides and matrix forming polymer such as polycarbophil, polyacrylate and polystyrene. This hydrocolloid hydrates and forms a colloidal gel barrier around its surface after coming in contact with gastric fluid and also helps in sustain releasing of drugs.

(ii) Microporous compartment system: In this technology a drug reservoir is encapsulated inside a microporous compartment with pores along its top and bottom walls [32]. The peripheral walls of the drug reservoir compartment are completely sealed. This sealing prevents any direct contact of gastric surface with the undissolved drug. The floatation chamber containing entrapped air allows the delivery system to aperture dissolves the drug and carries the drug for dissolved drug for continuous transport across the intestine for absorption.

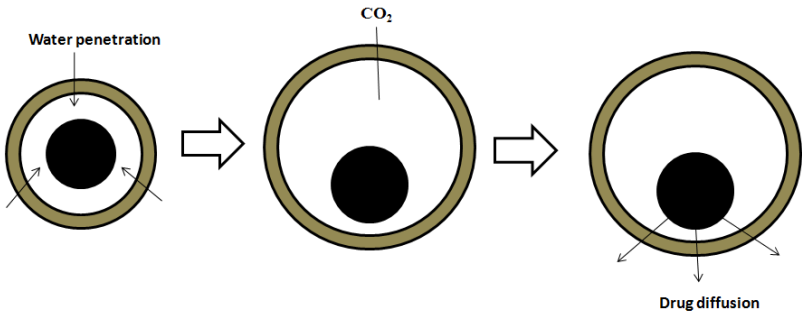
(iii) Alginate beads: To develop multi-unit dosage forms the freeze dried calcium alginate has been used [33]. Spherical beads of approximately 2.5 mm in diameter can be prepared by the precipitation of calcium alginate via dropping sodium alginate solution into aqueous solution of calcium chloride. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40°C for 24 hours, it leads to the formation of a porous system which can maintain a floating force for over 12 hours. These floating beads prolonged residence time for more than 5.5 hours.

(iv) Hollow microspheres / Microballons : A novel emulsion solvent diffusion method was used to prepare hollow microspheres loaded with drug in their outer polymer shelf [34]. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into agitated solution of poly vinyl alcohol (PVA) that was thermally controlled at 40°C. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed in the internal cavity of microsphere of the polymer and drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than12 hrs.

Effervescent systems

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan) and effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid) [35,36]. The system is so prepared that when it arrives in the stomach carbon dioxide is released, causing the formulation to float in the stomach.

Drug release from effervescent (gas generating) systems



This system can also be further described as:

(i)Volatile liquid containing systems: 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 PVA, 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 [37].

(ii)Gas-generating Systems: The effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2 occurred in this delivery system, which gets entrapped in the gelled hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chime[38]. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach used for the preparation of these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus carbon dioxide is released, causing the beads to float in the stomach .Other reported approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating mini-capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology etc [38].

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 [39].

Single-Unit Dosage Forms

Various types of tablets (bilayered and matrix) have been shown to have floatable characteristics. Some of the polymers used are hydroxypropyl cellulose, hydroxypropyl methylcellulose, crosspovidone, sodium carboxymethyl cellulose, and ethyl cellulose. Self-correcting floatable asymmetric configuration drug delivery system employs a disproportionate 3-layer matrix technology to control drug release. The use of large single-unit dosage forms sometime poses a problem of permanent retention of rigid large-sized single-unit forms especially in patients with bowel obstruction, intestinal adhesion, gastropathy, or a narrow pyloric opening (mean resting pyloric diameter 12.8 ± 7.0 mm). Floating dosage form should not be given to a patient just before going to bed as the gastric emptying of such a dosage form occurs randomly when the subject is in supine posture. One drawback of hydrodynamically balanced systems is that this system, being a matrix formulation, consists of a blend of drug and low-density polymers. The release kinetics of drug cannot be changed without changing the floating properties

of the dosage form and vice versa. 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.

Multiple-Unit Dosage Forms

The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the above mentioned disadvantages of single-unit formulations. In pursuit of this endeavor many multiple-unit floatable dosage forms have been designed. Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate. Spherical polymeric microsponges also referred to as "microballoons," have been prepared. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability [40]. In Carbon dioxide generating multiple-unit oral formulations [41] several devices with features that extend, unfold, or are inflated by carbon dioxide generated in the devices after administration have been described in the recent patent literature. These dosage forms are excluded from the passage of the pyloric sphincter if a diameter of ~12 to 18 mm in their expanded state is exceeded.

LIST OF DRUGS EXPLORED FOR VARIOUS FLOATING DOSAGE FORMS

1. **Microspheres Tablets / Pills:** Chlorpheniramine maleate, Aspirin, Griseofulvin, Terfenadine, Acetaminophen, p-nitroaniline, Acetylsalicylic acid, Ibuprofen, Amoxycillin trihydrate, Ampicillin, Tranilast, Atenolol, Theophylline, Captopril, Isosorbide dinitrate, Sotalol, Isosorbide mononitrate.
2. **Films:** P-Aminobenzoic acid, Cinnarizine, Prednisolone, Quinidine, gluconate.
3. **Granules:** Cinnarizine, Diclofenac sodium, Diltiazem, Indomethacin, Fluorouracil, Prednisolone, Isosorbide mononitrate, Isosorbide dinitrate.
4. **Powders:** Riboflavin phosphate, Sotalol, Theophylline.
5. **Capsules:** Verapamil HCl, Chlordiazepoxide HCl, Diazepam, Furosemide, L-dopa and benserazide, Misoprostol, Propranolol HCl, Ursodeoxycholic acid, Nicardipine [16,42].

Marketed preparations of Gastro retentive technologies available in the International Market [43,44]

Glumetza	Metformin	Polymer Based
proQuin XR	Ciprofloxacin	Polymer Based
Cifran OD	Ciprofloxacin (1g)	Gas generating Floating Form
GabapentinGR	Gabapentin (In Phase-III clinical trials) Accordion Pill TM	Polymer Based
Baclofen GRS	B aclofen	Coated multi-layer floating & swelling system
Coreg CR (Carvedilol)	Carvedilol	Gastro retention with osmotic system
Madopar	Levodopa and benserzide	Floating, CR Capsule
Topalkan	Aluminum magnesium antacid	Floating Liquid Alginate
Valrelease	Diazepam	Floating Capsule
Almagate flatcoat	Antacid	Floating Liquid Form
Liquid gavison	Alginic acid and sodium bicarbonate	Effervescent floating liquid alginate preparation
Cytotec	Misoprostol (100mcg/200mcg)	Bilayer Floating Capsule
Conviron	Ferrous Sulphate	Colloidal gel forming FDDS

GOOD CANDIDATES FOR GASTRORETENTIVE DRUG DELIVERY SYSTEM [45].

Drug	*Category*	*Half life*	*Peak time(hrs)*	*Bioavalibility*
Verapamil	*Calcium channel* blocker	6	1-2	20-35%
Nifedipine	Calcium channel blocker	2	0.5-0.2	45-65%
Omeprazole	Proton pump inhibitor	1-2	1	35-60%
Atenolol	Antihypertesive	4	3	40-50%
Propranolol	Antihypertensive	4-5	4	26%
Verapamil	Antihypertensive	6	1.8	35%
Diltiazem	Calcium channel blocker	3-4.5	50 min.	40%
Lidocaine	Local anaesthetic	1.5-2	4	35%
Clarithromycin	Antibiotic	3-4	2-2.5	50%
Ramipril	ACE inhibitor	2-4	3-5	28%

Characterization and Evaluation for FDDS

INVITRO METHODS

FOURIER *TRANSFORM INFRARED* ANALYSIS

Fourier transform infrared spectroscopy (FT-IR, Shimadzu, Model-RT-IR-8300) 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/cm2; the spectra were scanned over the wave number range of 3600 to 400 cm-1 at the ambient temperature[46].

DIFFERENTIAL SCANNING CALORIMETRY (DSC)

DSC (Shimadzu, Model-DSC-60/DSC-50/ Metler Toldeo) are used to characterize water of hydration of pharmaceuticals. Thermo grams of formulated preparations were obtained using DSC instrument equipped with an intercooler. Indium/Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample preparations were hermitically sealed in an aluminum pan and heated at a constant rate of 10°C/min; over a temperature range of 25° C – 65°C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50ml/min[46].

POWDER X-RAY DIFFRACTION

X-ray powder diffraction (Philips analytical, model-pw1710) 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 °C and 60 °C .The voltage and current used were 30KV and 30mA respectively[46].

SIZE AND SHAPE EVALUATION

The particle size and shape plays a major role in determining solubility rate of the drugs and thus potentially its bioavailability**.** The particle size of the formulation was determined using Sieve analysis (Jayant, Mumbai), Air elutriation (Bahco TM) analysis, Photo analysis, Optical microscope (Olympus (India) pvt.ltd), Electro résistance counting methods (Coulter counter), Sedimentation techniques, Laser diffraction methods, ultrasound attenuation spectroscopy, Air Pollution Emissions Measurements etc[15].

PARTICLE SIZE ANALYSIS, SURFACE CHARACTERIZATION (for floating microspheres and beads):

The particle size and the size distribution of beads or microspheres are 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) 32[47].

SURFACE TOPOGRAPHY

The surface topography and structures were determined using scanning electron microscope (SEM, JEOL JSM – 6701 F, Japan) operated with an acceleration voltage of 10k.v, Contact angle meter, Atomic force microscopy (AFM), Contact profiliometer[47].

FLOATATION STUDIES

The test for floating time is usually performed in simulated gastric fluid or 0.1 mole.lit^{-1} HCl maintained at 37° C, by using USP dissolution apparatus containing 900 ml of 0.1 molar HCl as the dissolution medium. 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[48].

SWELLING STUDIES

Swelling studies were performed to calculate molecular parameters of swollen polymers**.** Swelling studies was determined by using Dissolution apparatus, optical microscopy and other sophisticated techniques which include H1NMR imaging, Confocal laser scanning microscopy (CLSM), Cryogenic scanning electron microscopy (Cryo-SEM), Light scattering imaging (LSI) etc. The swelling studies by using Dissolution apparatus (USP dissolution apparatus USP-24) labindia disso 2000) was calculated as per the following formula. [49]

Swelling ratio = Weight of wet formulation / Weight of formulations

DETERMINATION OF THE DRUG CONTENT

Percentage drug content provides how much amount of the drug that was present in the formulation. It should not exceed 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 (ICPAES) and also by using spectroscopy techniques [50].

IN VITRO FLOATING AND DISSOLUTION BEHAVIOUR

The dissolution tests are generally performed on various drugs using USP dissolution apparatus. USP 28 states “the dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started”. A small, loose piece of nonreactive material with not more than a few turns of a wire helix may be attached to the dosage units that would otherwise float. However, standard USP or BP methods have not been shown to be reliable predictors of in vitro performance of floating dosage forms[51].

INVIVO METHOD

XRAY/GAMMA SCINTIAGRAPHY

X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage form nowadays. It helps to locate dosage form in the gastrointestinal tract (GIT), 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 radionuclide in a formulation allows indirect external observation using a γ-camera or scintiscanner. In case of γ-scintigraphy, the γ-rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GIT[47].

PHARMACOKINETIC STUDIES

Pharmacokinetic studies are an integral part of the in vivo studies and several works have been reported on these. Sawicki 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 tmax and AUC (0- infinity) values (3.75 h and 364.65ng/ml -1h respectively) for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets. (tmax value 1.21 h, and AUC value 224.22 mg/ml-1h) [47].

GASTROSCOPY

It comprises of peroral endoscopy, used with a fibereoptic and video systems. It is suggested that gastroscopy may be used to inspect visually the effect of prolonged stay in stomach milieu on the FDDS. Alternatively, FDDS may be drawn out of the stomach for more detailed evaluation[52].

ULTRASONAGRAPHY

Ultrasonic waves reflected substantially different acoustic impedances across interface enable the imaging of some abdominal organs. Most DFs do not have sharp acoustic mismatches across their interface with the physiological milieu. The characterization included assessment of intragastric location of the hydrogels, solvent penetration into the gel and interactions between gastric wall and FDDS during peristalsis[53].

RECENT ADVANCES IN STOMACH SPECIFIC FLOATING DOSAGE FORMS

Anand Patel et al developed a novel gastro retentive controlled release drug delivery system of Verapamil HCl in an effort to increase the gastric retention time of the dosage form and to control drug release. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. The optimized intragastric floating tablet composed of 3:2 of HPMC K4M to Xanthan gum exhibited 95.39% drug release in 24 h in vitro, while the buoyancy lag time was 36.2 sec, and the intragastric floating tablet remained buoyant for >24 h. X-ray studies showed that total buoyancy time was able to delay the gastric emptying of Verapamil HCl intragastric floating tablet in mongrel dogs for more than 4 h. [54].

Ravichandran Mahalingam, et al developed compacts containing selected bioadhesive polymers, fillers, and binders were investigated for their potential to deliver water soluble and water insoluble compounds in the stomach. Compacts with 90:10, 75:25, and 60:40 of polyvinylpyrrolidone (PVP) and polyethylene oxide (PEO) were evaluated for swelling, dissolution, bioadhesion, and in vitro gastric retention. Compacts containing higher PEO showed higher swelling (111.13%) and bioadhesion (0.62±0.03 N/cm2), and retained their integrity and adherence onto gastric mucosa for about 9 h under in vitro conditions. In vivo gastroretentive property of compacts were evaluated in Yorkshire cross swines. Compacts containing 58% PVP, 40% PEO and 2% of water soluble or water insoluble marker compounds showed gastro adhesive and retentive properties in vivo. It is concluded that PEO in combination with PVP yields a non disintegrating type bioadhesive dosage form which is suitable for gastroretentive applications[55].

Karunakar Neelam, et al designed the relative bioavailability of chlorothiazide from mucoadhesive polymeric compacts compared to commercial oral suspension in pigs. A single dose randomized study was conducted in 12 healthy pigs that are 9–10 weeks old. After overnight fasting, pigs were divided into two groups of six animals. To the first group, a reference product containing 50 mg of chlorothiazide suspension, and in the second group, test product mucoadhesive compacts chlorothiazide (50 mg) was administered with 75 ml of water via gastric tubes. Blood samples were collected between 0 to 24 h. Plasma was separated by protein precipitation, and

chlorothiazide concentrations were determined using a high-performance liquid chromatography method. The relative bioavailability of the compacts was lower than that of the suspension, and this may be due to the narrow window of absorption for chlorothiazide [56].

CONCLUSION

Drug absorption in the GIT is a variable process which depends upon gastric emptying and other physiological factors. FDDS promises to be a potential approach for gastric retention. Designing GRDDS requires a thorough understanding of the physicochemical properties of the drug, the physiological events of the GIT and formulation strategies. A careful consideration of the interplay of these parameters can help in designing a successful GRDDS. To formulate an efficient FDDS is sort of a challenge and the work will extend, until an ideal approach with industrial applicability and feasibility arrives Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing towards to commercialize this technique.

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