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GASTRORETENTIVE DRUG DELIVERY SYSTEM: AN APPROACH TO ENHANCE GASTRIC RETENTION FOR PROLONGED DRUG RELEASE

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Gastroretentive Drug Delivery System (GRDDS), Gastric Residence Time, (GRT), Physiology of Stomach, Floating and Non- Floating Systems

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ABSTRACT: Oral route has been the most convenient and accepted route of drug delivery. Owing to tremendous curative benefits of the oral controlled release dosage forms are being preferred as the interesting topic in pharmaceutical field to achieved improved therapeutics advantages. Gastroretentive drug delivery system is novel drug delivery systems which has an upper hand owing to its ability of prolonged retaining ability in the stomach and thereby increase gastric residence time of drugs and also improves bioavailability of drugs. Attempt has been made to summarize important factors controlling gastroretentive drug delivery systems. This review covers the advantages, disadvantages, marketed preparation and some patents of gastroretentive drug delivery system and represents the floating and non-floating gastroretentive system and also highlights some of the current gastroretentive approaches. Recent approaches to increase the gastric residence time of drug delivery systems include bioadhesive systems, floating systems (low density systems), non-floating systems (high density systems) , magnetic systems, swelling systems, unfoldable and expandable systems, raft forming systems and superporous systems, biodegradable hydrogel systems.

INTRODUCTION: Owing to tremendous curative benefits of the oral controlled release dosage forms are being preferred as the interesting topic of research over the past 3 decades [1]. The much obvious interest in this scenario is owing to its two fold advantage. Primarily, the oral controlled release dosage forms have the potential to upkeep an effective concentration in system for a longer duration.

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Secondly, it is helpful in providing easy dosage administration to the patient, that further provides patient compliance on the part of the patient and ultimately providing an array of options in the final formulation. But the benefits are yet obstructed by the knock of short gastric retention time (GRT) and the unpredictable rapid gastric rate may cause partial drug release in the absorption zone of the patient's body hence, hampering the efficiency of the dosage. It has caused the awaited development in oral gastroretentive drug delivery systems (GRDDS) [2].

An unaccustomed drug delivery system of gastroretentive dosage form has evolved. It has an upper hand owing to its ability of prolonged retaining ability in the stomach. This improves the

gastric residence span of drugs in stomach. This elongated retention ability provides more benefits which may be enumerated as: improving activity span for short half-life drugs, bioavailability of drugs, exclusion of side effects, reduction in dosage periodicity, saving drugs owing to former benefit, improves solubility for drugs that are less soluble in a high pH environment, optimized therapy and ultimately easy compliance on the part of the patient [3, 4].

Recent approaches to increase the gastric residence time of drug delivery systems include bioadhesive systems, floating systems (low density systems), non-floating systems (high density systems), magnetic systems, swelling systems, unfoldable and expandable systems, raft forming systems and superporous systems, biodegradable hydrogel systems [5].

Basic Gastrointestinal Tract Physiology: The stomach primarily aims at processing and transporting food. The stomach provides for short term food reservation and quick consumption of relatively large meal. The primary substantial metabolism of enzymes is promoted in stomach of proteins. The peristalsis of stomach mix up and grind consumed food with secretions of the stomach, turning food in simplified liquid form. The liquefied bulk is transported to the small intestine for further digestion [6].

The human anatomy categorises stomach in three main parts: fundus, body and antrum (pylorus). The proximal portion referred to as fundus and the body functions as storage for undigested food. The antrum provides for the main site for mixing motions and acts as gastric emptying pump by propeller actions [7].

Both the fasting and fed states cause gastric emptying. However the two states are varied upon pattern of motility. In this phenomenon, series of electric events takes place in cycles via stomach and intestine every 2 to 3hous [8]. There occurs a phenomenon of interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is divided in 4phases as given by Wilson and Washington [6]. The 4 phases are enumerated below and also shown in **Figure 1.**

1. Phase I- Basal phase, lasts from 30 to 60 minutes with rare contractions and is characterized by a lack of secretory, electrical, and contractile activity.

2. Phase II- Preburst phase, lasts for 20 to 40 minutes with intermittent contractions, during which contractile motions increase in frequency and size.

3. Phase III- Burst phase, lasts for 10 to 20 minutes with intense and regular contractions for short period, termed housekeeper waves that sweep off undigested food.

4. Phase IV lasts for 0 to 5 minutes and is the transition period between Phases III and I.

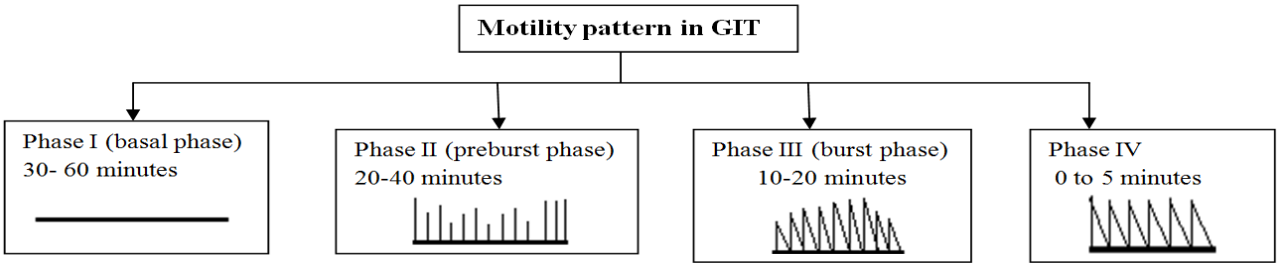

FIGURE 1: MOTILITY PATTERN IN GIT

Upon food being ingested, the stomach motions vary fasted to fed state. It's termed as digestive motility pattern and constitutes regular peristalsis as in phase II of the state of fast. This incredibly reduces food size (to less than 1mm), propelling food towards pylorus. The gastric emptying rate is delayed during fed state onset of MMC, causing slowdown of gastric emptying rate [9].

Why there is need of GRDDS? There occurs a quick elimination of certain drugs, that have been absorbed from the gastrointestinal tract (usually having short half-lives), from circulatory system due to which frequent dosing is required. To sort out this matter, innovative method gastroretentive drug delivery systems are incorporate.

They have efficient plasma drug concentration thereby reduce dosing frequency. Another highlight of this system is that it effectively reduces variations in plasma drug concentration by delivering the drug in a controlled and reproducible fashion [10]. The rationale for the use of GRDDS is shown in **Figure 2.**

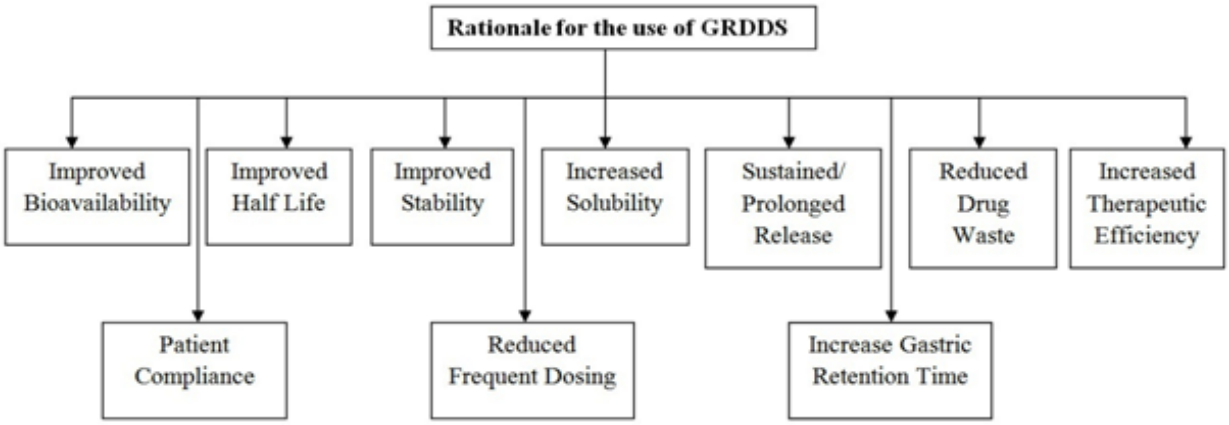

FIGURE 2: RATIONALE FOR THE USE OF GRDDS [11]

Advantages of GRDDS [12]:

1. Increase in bioavailability and curative efficiency of drugs and economic usage of dosage.

2. Minimised factor of risk in resistance in antibiotics owing to stabilised therapeutic levels over prolonged periods removing fluctuations.

3. Optimised release in case of short half-life drugs, causes flip flop pharmacokinetics and also ensures patient compliance with reduced dosage frequency.

4. They are advantageous against drawbacks of the gastric retention time (GRT) as well as the gastric emptying time (GET). The system remains buoyant on gastric fluid because of lower bulk density than gastric fluids.

5. These are efficient in repairing stomach and small intestine related problems. Its attributed to the fact that gastroretentive drug delivery sustains drug release and hence, avail local therapy in these organs.

6. This method provides with a systematic and controlled drug delivery system which minimises chances of drug over exposure at the diseased site.

7. Providing a narrow curative index, the gastroretentive dosage forms minimises variance in concentrations of drugs and effects.

8. This system provides higher efficiency due to reduced counter activity by body.

9. As the system provides with controlled rates of fluctuation, a wider array is provided for selectivity in receptor activation.

Disadvantages of GRDDS [13, 14, 15]

1. Need for increased level of fluids in the stomach.

2. Unsuitable for such drugs as:

    - Problematic with solubility in gastric fluid
    - Causing G.I irritation
    - Inefficient in acidic environment

3. Drugs intended for selective release in the colon.

4. Unpredictable adherence owing to state of constant renewal of mucus wall of stomach.

5. GRDDS is fed into the system after the meal as time of stay in stomach depends on digestive state.

6. The ability of the drug to remain in the stomach depends upon the subject being positioned upright.

7. Hydrogel based swelling system takes longer time to swell.

8. Upon multiple administrations, size increasing drug delivery systems pose the threat to life owing to possible hazard of permanent retention in stomach.

9. Superporous systems having drawback like problematical storage of much easily hydrolysable, biodegradable polymers.

Suitable and unsuitable drugs candidates for GRDDS: Suitable and unsuitable drugs candidates for GRDDS are listed in **Table 1** and **Table 2** respectively.

TABLE 1: POTENTIAL DRUG CANDIDATES FOR GRDDS [16]

S. No.	Suitable Drug candidates	Example
1.	Drugs acting locally in the stomach.	Antacids, Anti-ulcer drugs, drugs against *H. Pylori*, Misoprostol, Clarithromycin, Amoxicillin.
2.	Drugs with narrow absorption window in Gastrointestinal tract (GIT).	Cyclosporine, Methotrexate, Levodopa, Repaglindine, Riboflavin, Furosemide, Para-aminobenzoic Acid, Atenolol, Theophyllin,
3.	Drugs having unstable properties in the intestinal or colonic environment.	Captopril, Ranitidine HCl, Metronidazole, Metformin HCl.
4.	Drugs caused imbalance of normal colonic microbes.	Antibiotics against *H. Pylori*, Amoxicillin Trihydrate.
5.	Drugs having low solubility at high pH values.	Diazepam, Chlordiazepoxide, Furosemide, Verapamil HCl.

TABLE 2: UNSUITABLE DRUG CANDIDATES FOR GRDDS [17]

S. No.	Unsuitable Drug Candidates	Example
1.	Drugs having very limited acid solubility.	Phenytoin
2.	Drugs that exhibits instability in the gastric environment.	Erythromycin
3.	Drugs that are used for selective release in the colon.	5- amino salicylic acid and corticosteroids

Factors controlling GRDDS [9, 18, 19]: Factors controlling GRDDS are shown in **Figure 3** and some of the factors are enumerated below:

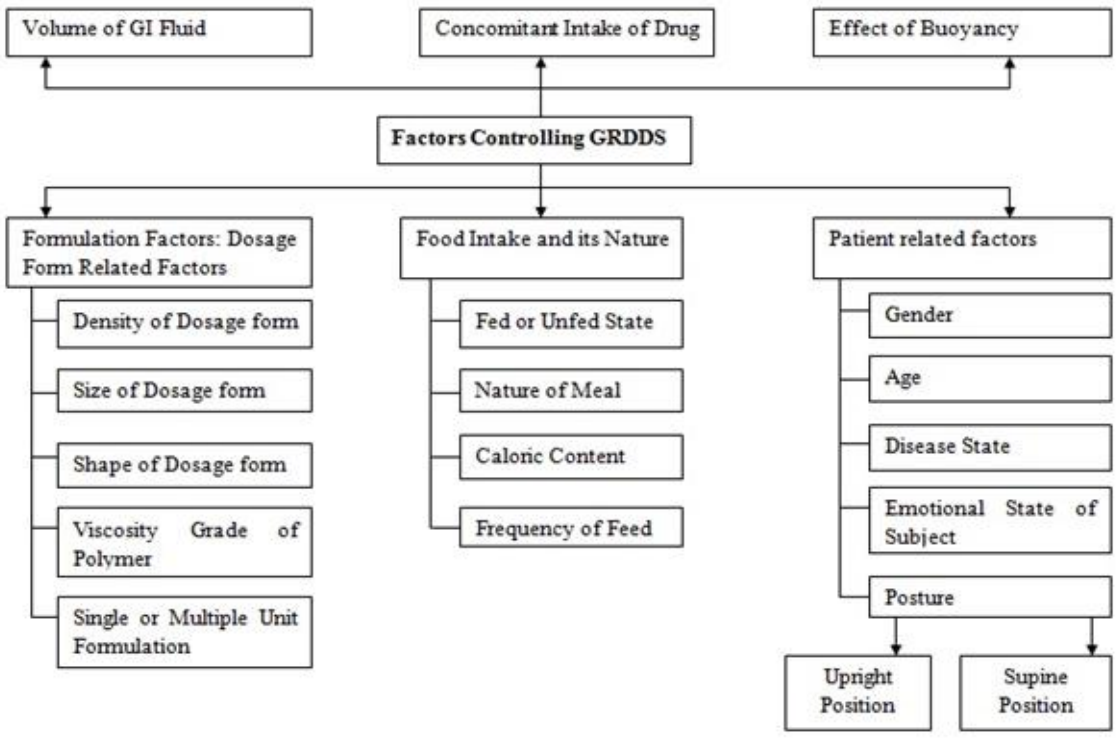

FIGURE 3: FACTORS CONTROLLING GRDDS

1. **Density:** Dosage form with lower density in the gastric content can float to the surface while high density sink to the bottom of the stomach. Suitable density required for floating property is less than 1.0 gm/ cm^3

2. **Size:** Size should be more than 7.5 mm in diameter.

3. **Shape:** Either round or spherical shaped dosage form exhibit better property related to other shapes.

4. **Single or multiple unit formulation:** Multiple units are desirable due to foretell release profile.

5. **Fed or Unfed State:** Gastric retention time is less during fasting condition due to rise in gastric motility

6. **Nature of Meal:** High amount of fatty acid and other indigestible polymers slow down the gastric retention time due to variation in gastric motility

7. **Frequency of Feed:** Low frequency of migrating myoelectric complex (MMC) contributes to GRT upto 400 times which inturn depends on the frequency of food intake

8. **Caloric Content:** A high protein and fat rich diet can increase GRT by 4 to 10h.

9. **Gender:** Males have greater GRT than females

10. **Age:** GRT is more in geriatric patients and less in neonates and children. Age above 70 (>70) exhibit longer GRT.

11. **Posture:** GRT can vary between supine and upright ambulatory states of the patient.

12. **Disease State:** Gastric disease such as diabetes, chron's disease, hypothyroidism, hyperthyroidism, duodenal ulcers etc fluctuates the GRT

13. **Concomitant Intake of Drug:** Combination of some drugs along with gastric motility enhancers or depressants, affect GRT

Approaches for GRDDS: The following methods have been devised to improve period of retainment of oral dosage form in the stomach viz. floating system, swelling and expanding system, bioadhesive system, high density system and other delayed gastric emptying devices [10]. It is shown in Figure 4 and classification of GRDDS is shown in **Figure 5.**

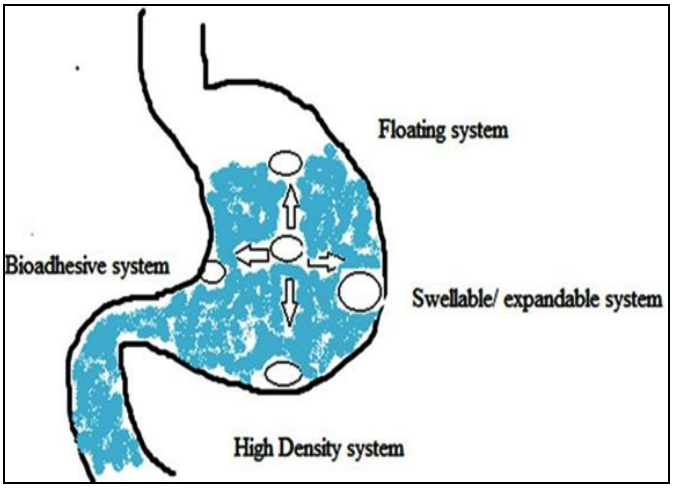

FIGURE 4: APPROACHES FOR GRDDS

1. **Floating Systems:** An optimised level of drug bioavailability can be reached by judicious gastric retention. The floating drug delivery system is a novel approach for the same. It is needed for drugs that have an absorption window in the stomach or in the upper small intestine [21]. This method does not affect the rate of gastric emptying over a prolonged time. It is a low density approach (lower than gastric fluid). Hence remain buoyant in the stomach releasing the drug slowly. The emptying of residual system is followed by the drug release, from the stomach. Thus occurs an increased gastric retention time (GRT) and improved control over fluctuating plasma drug concentration [13]. The pre-requisites for floating drug delivery system are [21]:

   a. Slow content release to act as reservoir.

   b. Specific gravity should be maintained lower than gastric contents (1.004 – 1.01 gm/cm3)

   c. It must form a cohesive gel barrier.

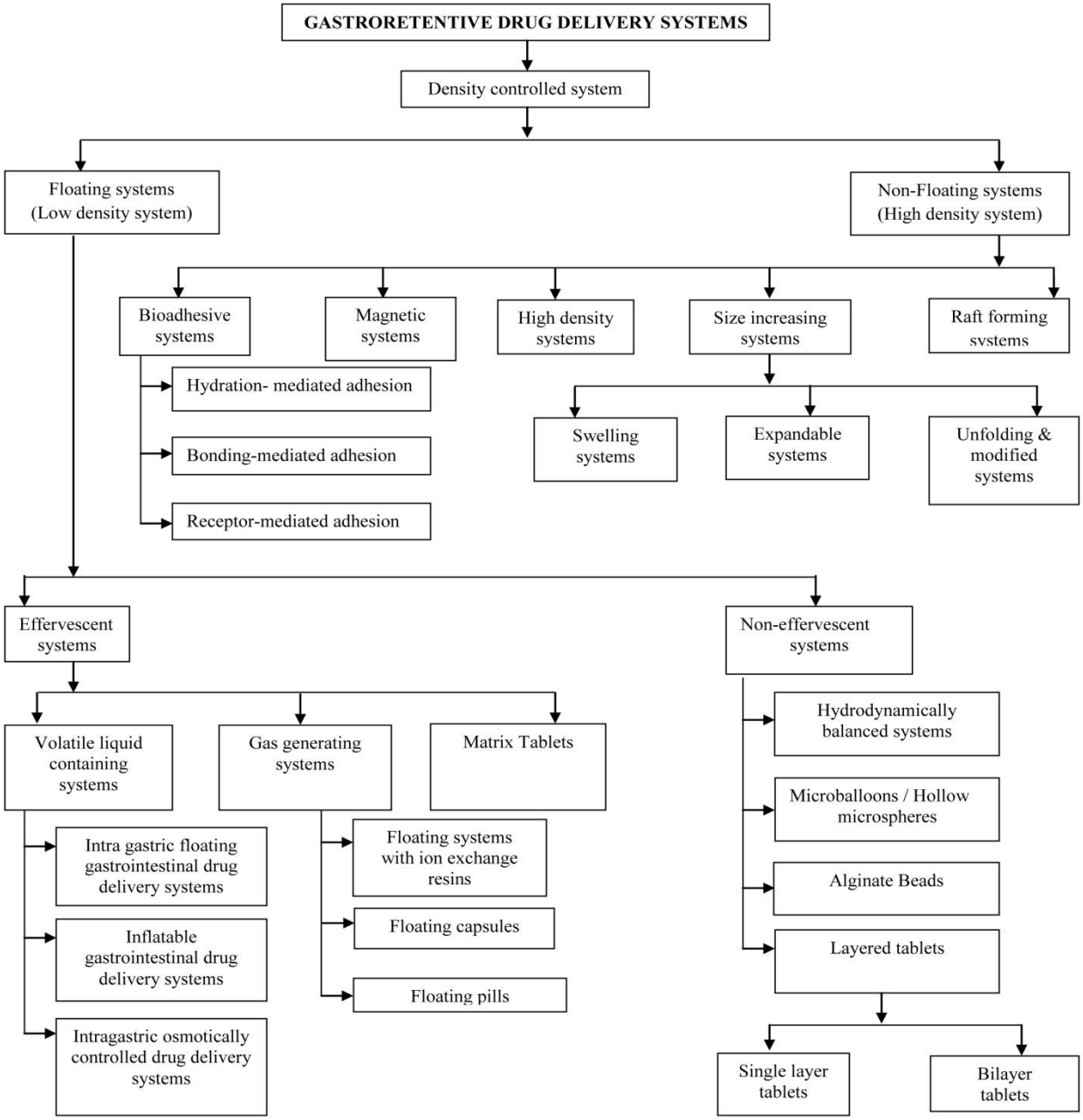

FIGURE 5: CLASSIFICATION OF GRDDS [10, 20]

Mechanism of Floating Drug Delivery Systems: The slow drug release is accompanied with requisite rate during the system flow on the gastric contents. The release is followed by removal of the residual system from the stomach. But, along with the appropriate level of floating force (F), minimum levels of gastric contents are needed to permit achievement of buoyancy retention principle and also to keep dosage form buoyant over meal surface. In the literature an apparatus has been described that measures the kinetics of floating force. Its operation constitutes of measuring a force equivalent to F (with respect to time) which keeps the object submerged.

As depicted in **Figure 6,** the presence of force F in a higher positive side makes the object flow better. This apparatus optimizes FDDS and prevents its drawbacks unforeseeable intragastric buoyancy capability variations, related to stability and durability [22].

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

$$= (D_f - D_s)\, gv$$

Where, F= total vertical force, D_f = fluid density, D_s = object density, v = volume and g = acceleration due to gravity.

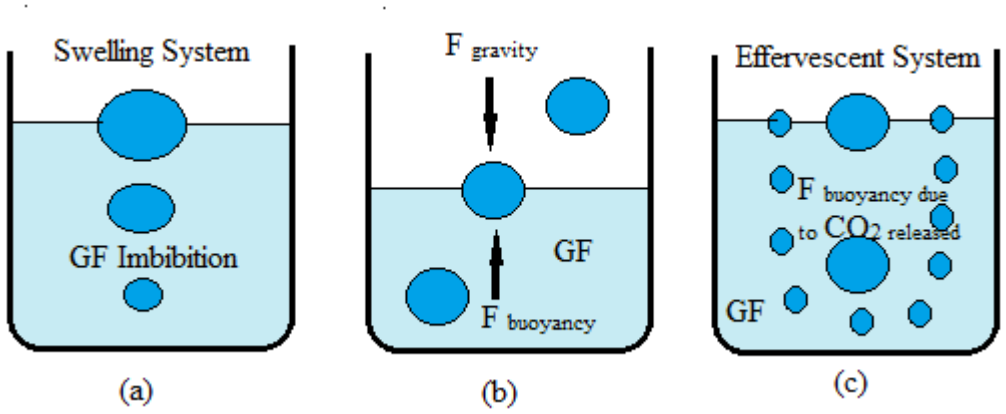

FIGURE 6: MECHANISM OF FLOATING DRUG DELIVERY SYSTEMS, GF: GASTRIC FLUID, CO_2: CARBON DIOXIDE

Based on the buoyancy mechanism, floating systems are classified as follows:

I. Effervescent systems

II. Non-effervescent systems

I. **Effervescent Systems (Gas Generating Systems):** Gas bubble generation helps to achieve floatability. The swellable polymers viz. methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid and citric acid, help in creating matrix type of such systems [23]. They are created in a manner that upon contact with gastric contents CO_2 is released finally entrapping in swollen hydrocolloids, that makes dosage forms buoyant [13].

These systems are further classified as below:

A. **Volatile Liquid Containing System:** This system comprises of dual chambers having an impermeable, pressure responsive, movable bladder separation. The former chamber has drugs and the latter has volatile liquid. To sustain the GRT of a drug delivery system an inflatable chamber has to be incorporated, that carries a liquid e.g. ether, cyclopentane. It turns to gaseous form at body temperature causing inflatation of the chamber in the stomach. It may contain a biodegradable plug, made of polyvinyl alcohol, polyethylene, etc. This plug gradually dissolves making the chamber release gas and to collapse after a specific duration to allow spontaneous release of the inflatable systems from the stomach. The drug continues to release as the device inflates [24].

These systems are further classified as below:

a. Intragastric floating gastrointestinal drug system.

b. Inflatable gastrointestinal delivery system

c. Intragastric-osmotically controlled drug delivery system

B. Matrix Tablets: It can be formulised in a single layer matrix table by implementing bicarbonates in the matrix forming hydrocolloid gel agent or in a dual layer matrix along with gas generating matrix together as an individual layer. The drug acts as the second layer. There is a possibility of triple layer matrix tablet. However now the gas generating matrix is one layer and rest two are drug layers [10].

C. Gas Generating Systems

a. Floating capsules

b. Floating pills

c. Floating system with ion exchange resins

II. **Non- effervescent Systems:** The Non-effervescent floating dosage forms have swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymeth-

acrylate, and polystyrene [25]. Its creation has a simplistic approach i.e. mixing of drug with the gel, followed by swelling by coming in contract with gastric fluid after oral administration and thus maintaining a relative integrity of shape and keeping a bulk density less than one (<1) [25, 26]. The dosage form gains its buoyancy owing to air trapped in the swelled up matrix. This swollen up matrix reserves drug and maintains sustained drug release via gelatinous mass [25]. Hydroxylpropyl methyl cellulose (HPMC), polyacrylate, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates, are the most commonly used excipients [26].

These systems are further classified as below:

A. Hydrodynamically balanced systems

B. Microballoons / hollow microspheres

C. Alginate beads

D. Layered tablets

   a. Single layered floating tablets

   b. Double layered floating tablets

Table 3 enlists examples of commonly used drugs in formulation of different forms of GRDDS.

TABLE 3: COMMONLY USED DRUGS IN FORMULATION OF GRDDS

Tablets	Cephalexin, Ziduvudine, Losartan, Pentoxyfillin, Cholrpheniramine maleate, Theophylline, Furosemide, Ciprofloxacin, Captopril, Acetylsalicylic acid, Nimodipine, Amoxycillin trihydrate, Cinnarazine, Dilitiazem, Florouracil, Piretanide, Prednisolone, Riboflavin- 5`Phosphate, Metformin Hydrochloride, Atenolol, Diltiazem, p- Aminobenzoic acid(PABA), Verapamil HCI, Isosorbide di nitrate, Sotalol, Isosorbide mononitrate, Aceraminophen, Ampicillin.
Capsules	Nicardipine, L-Dopa and benserazide, chlordizepoxide HCI, Furosemide, Misoprostal, Diazepam, Propranlol, Urodeoxycholic acid, Pepstatin, Celiprolol HCl.
Microspheres	Verapamil, Aspirin, Griseofulvin, and p-nitroanilline, Ketoprofen, Tranilast, Iboprufen, Terfenadine, Piroxicam, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol, Rosiglitazone maleate, Flurbiprofen, Orlistat.
Granules	Indomethacin, Diclofenac sodium, Prednisolone, Cinnarizine, Diltiazem, Fluorouracil , Isosorbide mononitrate ,Isosorbide dinitrate, Ranitidine HCl.
Films	Drug delivery device, Albendazole, P-aminobenzoic Acid, Piretanide, Prednisolone, Quinidine gluconate, Cinnarizine.
Powders	Several basic drugs-Riboflavin, Sotalol, Theophylline.
Bilayer tablet	Misoprostal, Trimetazidine hydrochloride and Metoprolol succinate, Diltiazem HCI and Lovastatin, Atenolol.
Beads	Ranitidine HCl, Loratadine, Curcumin β-cyclodextrin complex, Diltiazem HCl.

2. **Non-floating Systems:** Non- floating systems are class of gastroretentive drug delivery systems which do not float but remain in the stomach for a prolonged time period. These systems are further classified as below and some of them are described in **Table 4.**

   A. Bioadhesive systems

   B. Swelling systems

   C. High density systems

   D. Expandable systems

   E. Magnetic systems

   F. Raft forming system

   G. Superporous hydrogel systems

Gastroretentive Drug Delivery System: Review from previous studies: Review from previous studies of GRDDS is listed in **Table 5.**

Marketed products and patents of GRDDS: Marketed products and patents of some gastroretentive drug delivery systems are listed in **Table 6** and **Table 7** respectively.

TABLE 4: NON-FLOATING SYSTEMS

Non-Floating Systems	Mechanism	Polymer/ Material Used
Bioadhesive Systems [27, 28]	Bioadhesive systems adhere to the biological membrane (mucosa) of the stomach and maintain intimate contact with the membrane for a longer time and hence retains in stomach for its prolonged release.	Polycarbophil , Carbopol, Lectins, Chitosan, Carboxy Methyl Cellulose, Gliadin, Polyethylene Glycol, Tragacanth, Dextrin, Chitosan, Sodium Alginate, Cholestyramine, Cholestyramine, Poly Acrylic Acid, Hydroxypropyl Methylcellulose, Sucralfate.
Swelling Systems ('plug type systems') [29, 30]	After being swallowed, these dosage forms swell to a size that prevents their passage through the pylorus.	Acacia, Pectin, Chitosan, Agar, Casein, Bentonite, Veegum, Hydroxy Propyl Methyl Cellulose (HPMC) (K4M, K100M and K15M), Gellan gum, Sodium Carboxy Methyl Cellulose (CMC), Methyl Cellulose (MC), Hydroxy Propyl Cellulose (HPC).
High Density Systems [31, 32]	These systems possess density greater than the gastric fluids due to which the system sinks to the bottom and remains in the stomach.	Zinc Oxide, Titanium Dioxide, Iron Powder, Barium Sulphate.

TABLE 5: REVIEW FROM PREVIOUS STUDIES OF GRDDS

Delivery System	Drug	Polymer	Method
Floating Tablets [33]	Diltiazem Hydrochloride	Xanthan Gum, Karaya Gum, Guar Gum, Carrageenan	Wet Granulation Method
Floating Tablets [34]	Metoprolol Tartarate	Hydroxypropyl Methylcellulose (HPMC K4M, HPMC K100M)	Direct Compression Method
Floating Tablets [35]	Ritonavir	HPMC E15LV, HPMC E50LV, HPMC K100LV, HPMC K4M, Polyvinyl Pyrrolidone (PVP K30)	Direct Compression Method
Floating Microspheres [36]	Valacyclovir Hydrochloride	Ethylcellulose	Water-In-Oil (W/O) Emulsification Solvent Evaporation Method
Floating Tablets [37]	Ranitidine Hydrochloride	HPMC K15M, HPMC K100M, Polyethylene Oxide (Polyox WSR303)	Dry Granulation Method
Floating Matrix Tablet [38]	Stavudine	HPMC K4M, HPMC K15M, HPMC K100K, Ethyl Cellulose	Melt Granulation Method
Floating Tablet [39]	Quetiapine Fumarate	HPMC K15M, Carbopol, Sodium Carboxymethyl Cellulose, PVP K30	Wet Granulation Method
Superporous Hydrogel [40]	Ranitidine Hydrochloride	HPMC, Carbopol 934P, Ethyl Cellulose, Chitosan, Sodium Carboxymethyl Cellulose	Superporous Hydrogel Composite
Floating Microballoons [41]	Metformin	HPMC K4M, Ethyl Cellulose	Solvent Evaporation Method
Hollow Microspheres [42]	Famotidine	Eudragit RL100, Cellulose Acetate	Emulsion Solvent Diffusion Method
Floating Tablets [43]	Famotidine	Gelucire 43/01, HPMC K4M	Solvent Free Melt Granulation Method
Mucoadhesive Tablets [44]	Venlafaxine Hydrochloride	Carbopol 971P, Ethyl Cellulose, Eudragit RS-PO	Direct Compression Method
Floating Matrix Tablets [45]	Ciprofloxacin Hydrochloride	HPMC K15M, Sodium Alginate	Direct Compression Method
Floating Tablets [46]	5-Fluorouracil	Carbopol 934P, HPMC K4M, HPMC K15M	Wet Granulation Method
Sustained Release Tablets [47]	Ofloxacin	Psyllium Husk, HPMC K100M, Crospovidone	Wet Granulation Method
Floating Tablets [48]	Ranitidine Hydrochloride	HPMC K4 M, Guar Gum, Xanthan Gum	3^2 Full Factorial Design

TABLE 6: COMMERCIALLY AVAILABLE MARKETED PRODUCTS OF GRDDS

Brand Name	Drug	Dosage forms	Dose	Indications	Company
Cifran O.D	Ciprofloxacin	Tablet	500mg, 1 gm	Systemic treatment of infections	Ranbaxy, India
Liquid Gavison	Al hydroxide and Mg carbonate	Liquid	95mg and 358 mg respectively	Antacid	Glaxo Smith Kline, India
Madopar	Levodopa and Benserazide	Capsule	100mg and 25mg respectively	Parkinson's disease	Roche Products, USA
Glumetza	Metformin Hydrochloride	Tablet	500mg and 1000mg	Type 2 diabetes	Depomed, Canada
Valrelease	Diazepam	Capsule	15 mg	Anxiety disorders, alcohol withdrawal symptoms, muscle spasms.	Hoffmann-LaRoche, USA
Topalkan	Aluminium – Magnesium antacid	Liquid alginate	----------	Antacid	Pierre Fabre Drug, France
Cyotec	Misoprostal	Bilayer capsule	100 mcg/200 mcg	Used with nonsteroidal anti-inflammatory drug to prevent gastric ulcers.	Pharmacia, USA
Conviron	Ferrous sulphate	Colloidal gel	----------	Antianaemic	Ranbaxy, India
Oflin OD	Ofloxacin	Tablet	400mg	Genito urinary, respiratory, gastro intestinal, skin and soft tissue infections.	Ranbaxy, India

TABLE 7: PATENTS FOR GRDDS [49-60]

US Patent /App. No.	Patent Title	Issue/Publication Date	Patent Owner
2013/0078,290	Gastroretentive Dosage Forms of GABA Analogs	Mar 28, 2013	Rubicon Research Private Limited
2013/0022,654	Controlled Release Pharmaceutical Compositions of Tapentadol	Jan 24, 2013	Lupin Limited
2013/0004,434	Gastroretentive, Extended Release Composition of Therapeutic Agent	Jan 3, 2013	Council of Scientific And Industrial Research
2012/0321,706	Novel Gastroretentive Dosage Forms of Poorly Soluble Drugs	Dec 20, 2012	Intec Pharma Ltd.
2012/0269,866	Gastroretentive Composition on the Basis of a Water-Soluble Reaction Product from a Vinyl Group-Containing Precursor	Oct 25, 2012	Basf Corporation
2012/0021,051	Zaleplon Gastroretentive Drug Delivery System	Jan 26, 2012	Intec Pharma Ltd.
2011/0268,666	Novel Gastroretentive Delivery System	Nov 3, 2011	Intec Pharma Ltd., Yissum Research Development Company of the Hebrew University of Jerusalem,
2011/0171,275	Gastroretentive Drug Delivery System, Preparation Method and Use Thereof	Jul 14, 2011	Team Academy of Pharmaceutical Science
2007/0128,276	Controlled Release Compositions Comprising Nimesulide	Jun 7, 2007	Panacea Biotec Limited
2006/0121,106	Therapeutic System Comprising Amoxicillin and Clavulanic Acid	Jun 8, 2006	Lek Pharmaceuticals D.D.
2004/6,685,962	Gastroretentive Controlled Release Pharmaceutical Dosage Forms	Feb 3, 2004	Yissum Research Development Company of the Hebrew University of Jerusalem
2003/0021,845	Gastroretentive Controlled Release Pharmaceutical Dosage Forms	Jan 30, 2003	Yissum Research Development Company of the Hebrew University of Jerusalem

CONCLUSION: Gastroretentive drug delivery system have emerged as an efficient means of prolonged retaining ability in the stomach and thereby increase gastric residence time of drugs and also improves bioavailability of drugs. Inspite of number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focussing towards commercializing this technique. Number of commercial products and patents issued in this field are evident of it.

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