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A Review On Current Perspective Of Gastroretentive Drug Delivery Systems Prioritising Floating Dosage Forms

Güncel Bakış Açısı ile Yüzen Dozaj Formlarına Öncelik Vererek Gastroretentif İlaç Salım Sistemlerinin Derlemesi

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ABSTRACT

Current pharmaceutical approaches continue to favour oral dosage delivery systems above all other routes. This is due to ease of administration and increase in patient complaisance. A common objective of a drug delivery systems is to achieve a drug that could be taken in a single dosage form. Yet, drug delivery mechanisms generally lack certain characteristics such as an adequate oral bioavailability and a prolonged half-life. Floating drug delivery systems (FDDS) are systems that are a part of gastroretentive drug delivery systems (GRDDS) with low density that has floating ability over the gastric contents of the stomach. Floating dosage forms are taken orally and developed to increase the transit time of the active substance through the gastrointestinal tract and to achieve a systemic effect. The taken drug will remain at floating state in the stomach for an extended period without affecting the gastric emptying rate. FDDS provides an efficient method for improving the drug's bioavailability, reducing drug waste and providing controlled drug delivery systems. This review will generally focus on FDDS as a GRDDS and classify alternative systems, such as non-floating systems, and briefly mention excipients used in order to obtain an effective gastroretentive system.

Keywords: Floating Drug Delivery Systems (FDDS), Gastroretentive Drug Delivery Systems (GRDDS), Gastric Content, Non-Floating Drug Delivery Systems, Effervescent Systems, Non-effervescent Systems

ÖZ

Mevcut farmasötik yaklaşımlarda, diğer tüm yollarından farklı olarak halen oral dozaj formları tercih edilmeye devam etmektedir. Bunun nedeni uygulama kolaylığı ve hasta uyuncunun yüksek olmasıdır. İlaç salım sistemlerinin ortak amacı, ilacın tek bir dozaj formu olarak alınabilmesini sağlamaktır. Yine de, ilaç salım mekanizmaları genellikle uygun bir biyoyararlanım ve uzatılmış yarı ömür gibi özelliklerden yoksundur. Yüzebilen ilaç salım sistemleri (FDDS), mide içeriği üzerinde kalabilme özelliğine sahip, düşük yoğunluklu olan sistemlerdir ve gastroretentif ilaç salım sistemlerinin (GRDDS) bir parçası olarak değerlendirilirler. Yüzebilen dozaj formları ağızdan alınır ve etken maddenin gastrointestinal sistemden geçiş süresini uzatarak lokal/sistemik etki elde etmek için geliştirilirler. Söz konusu ilaç mide boşalma hızını etkilemeden uzun süre midede yüzer halde kalır. FDDS ilaç biyoyararlanımını iyileştirir, ilaç israfını azaltır ve kontrollü ilaç salım sistemi etkisini sağlamak için etkili bir yöntem olarak değerlendirilir. Bu derleme, genellikle bir gastoretentif ilaç sistemlerinden birisi olan yüzebilen dozaj formlarına odaklanmıştır ve özetle gastrik sistemde kalabilen alternatif sistemlerden ve bu sistemleri geliştirmek için kullanılan eksipiyanlardan bahsedecektir.

Anahtar Kelimeler: Yüzebilen İlaç Salım Sistemleri (FDDS), Gastroretentif İlaç Salım Sistemleri (GRDDS), Gastrik İçerik, Yüzmeyen İlaç Salım Sistemleri, Efervesan Sistemler, Efervesan Olmayan Sistemler

INTRODUCTION

Compliance is immensely dependent on the ease of drug administration. A patient is more likely to adapt to medication when it does not interfere with the person's daily activities. To date, oral dosage forms remain the ideal route of administration. This is due to many factors including easy storage and transport of drug, controlled delivery, flexibility in formulation and generally reduced pricing when compared to other dosage forms. The common objective of drug delivery systems is to achieve a systematic drug that could be taken as a single dosage form. Especially when the drug in question is to be taken periodically throughout the patient's life. An incorporated single unit dosage form would also reduce the frequency of medical administration. It should also be noted that even though it is the easiest form of drug delivery, in case of emergencies oral dosage forms are not applicable due to their slow absorption rate.

Oral drug delivery systems have a complex absorption mechanism. The drug should be soluble in gastric fluid in order for absorption in the stomach, small intestine or colon. An orally taken drug can be absorbed in four different types of pathways: Carrier-mediated transcellular, facilitated transport, transcellular and paracellular. Transcellular pathway is the main mechanism that is being favoured. Also, environmental factors such as the pH of stomach content, length of the segment, thickness of mucus, bacterial diversity in different segments and residence time of the drug influences absorption (1). Lately, there has been an increased demand for oral forms of medications used, especially for chronic diseases. This is where the importance of alternative technological approaches come into the picture.

This review will cover the GRDDS approaches used for oral administration and provide information on suitable drug candidates and factors affecting the efficiency of the system. The main focus will be around FDDS and approaches used in order to achieve prolonged drug systems in the gastric environment. In addition, anatomy and the physiological state of the stomach, non-floating systems, challenges of floating dosage forms, and excipients used will be discussed.

1. Anatomy and Physiology of the Gastrointestinal Tract

In order to formulate a successful system, it is indispensable to understand the anatomy of the stomach and its physiology. The stomach is composed of following 3 parts: body, fundus and antrum (pylorus). The fundus is the proximal part of the stomach that allows accumulation of stomach gases produced by chemical digestion. The body, also called the corpus, helps in the storage of ingested materials. Whereas; the pylorus is found as an anatomical sphincter that is located between the most terminal antrum, and the duodenum provides the major site for mixing motions which serves as gastric emptying pump. It acts as a sieve and has a mechanical structure to the passage of large particles. The open pylorus has a diameter of around 15 mm in humans. A drug system that has a greater size than this will have problems passing into the small intestine. The fundus and body parts of the stomach mainly act as a holder for undigested food. On the other hand, the antrum has a pump like activity when it comes to assisting the gastric emptying process (2,3,4).

The passage state of the drug from stomach to the small intestine is named gastric emptying. Gastric emptying occurs both during fasting and in fed states. In cases where the drug is degraded in a gastric environment, faster gastric emptying rate enhances the bioavailability of the drug. On the other hand, for poorly soluble drugs and drugs that are mostly absorbed from the stomach or proximal part of the intestine, the delayed gastric emptying promotes the disintegration process. Interdigestive myloelectric cycle or migrating myloelectric cycle (MMC) is the flexible pattern of the stomach and occurs when in fasting state an indigestive series of electrical events takes place. This cycle occurs once in every 2 to 3 hours. This formation could be divided into 4 consecutive phases (3) (Figure 1):

Phase 1 (basal phase): Lasts from 30 to 60 minutes with rare contractions (Quiescent period).

Phase 2 (pre-burst phase): Lasts for 20 to 40 minutes with intermittent action potential and contractions. The concentration and frequency increase perceptibly with phase progression. Bile secretion and mucus discharge occurs.

Phase 3 (burst phase): Lasts for 10 to 20 minutes and includes intense and steady contractions for a brief period. This wave permits undigested material to exit out of the stomach down to the small intestine (also known as the housekeeper wave). Mucus discharge and a force of contraction takes place.

Phase 4: Known as a period of transition from phase 3 and phase 1, and last for 0 to 5 minutes.

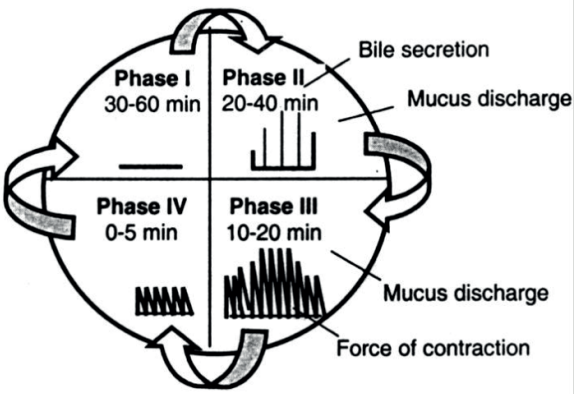

Figure 1. Gastrointestinal motility (3).

Following the ingestion of a meal, the motor activity in the fed state is reduced for 5-10 min and lasts as long as food remains in the stomach. The period of fed activity extends longer with large amounts of food ingested (5).

2. Gastroretentive Drug Delivery Systems (GRDDS)

A reduced frequency of administration is achieved by achieving prolonged release mechanisms. Regarding this, oral controlled release (CR) techniques have been used in formulations these past four decades due to their appreciable therapeutic advantages (6). However, techniques like CR lacks the ability to keep formulation within the desired range of gastrointestinal tract (GIT). This inevitably leads to incomplete drug absorption and lower therapeutic responses. Another main problem faced with oral dosage use is the short gastric retention time (GRT). The rapid gastric rate is unpredictable and may lead to partial drug release in the absorption zone. Gastric emptying is an extremely variable process for dosage forms (7). Thus, the search for alternative and improved delivery techniques begun. GRDDS is one of the leading approaches used in order to improve the bioavailability of drugs that are active locally inside the stomach. This technology has gained unquestionable attention these past three decades. GRDDS uses prolonged and controlled drug release strategies. Owing to this, the formulations used should have a moderate but exhaustive drug release in the stomach. The aim is improved bioavailability with lower pharmaceutical doses, a better availability of new products and minimised gastrointestinal side effects (8-10).

Several factors should be highlighted when preparing a pharmaceutical dosage form for gastrointestinal tract. These could be summarised as (11):

-Gastric emptying is controlled by feeding status.

-An object that has a size <10 mm is able to exit a fed state of the stomach.

-An object with a size >20 mm will be kept in the fed state of the stomach.

-The transit inside the colon is lengthy (around 20 hours).

-The transit time inside the small intestine is around 3 hours.

-A drug formulation can reach the colon within 4 to 5 hours in fasted subjects.

3. Floating Drug Delivery Systems

Many attempts have been made to develop GRDDS. There are several techniques stated in literature to develop a dosage form that retains inside the stomach for a prolonged time. This review will mainly focus on floating drug delivery systems. Examples for other techniques used in GRDDS include swelling systems, mucoadhesive systems, super-porous hydrogels, hydro-dynamically balanced systems, non-floating systems (high density systems), ion exchange resins, and magnetic systems.

The concept of FDDS was first described by Davis in 1968 as a disclosed method to overcome the difficulties some patients experienced when taking oral medicine. FDDS can be described as low-density

systems that have a bulk density less than that of the gastric fluid found inside the stomach. Thus, these systems are able to float for a prolonged period of time in the stomach. They are generally unaffected by the gastric emptying rate. The dosage system slowly releases the desired rate from the formulation. Afterwards, the residual system gets emptied from the stomach leaving its environment. This shows an increased GRT along with an increased control of the fluctuations in plasma drug concentration. A floating form has the potential to emerge as a novel dosage form. In theory, it solves the problems faced with oral medications and has the power to keep an efficient concentration of the system for longer durations. Floating systems possess multiple challenges following administration. First of all, insufficient floatation occurs in cases where the fluid level is low inside the stomach. Second, the dosage forms gets transited to the pylorus by forced house-keeping waves. Such occurrences inevitably lead to a reduced floating time and a limited retention of the dosage form (12-15).

Floating systems are found as single-unit or multiple-unit dosage forms. A single-unit system could be fallible in prolonging the gastric stay time due to the systems 'all or nothing' concept of emptying process. Whereas multiple-unit systems appear to be effectively suited since they claim to reduce the inter-subject variability in absorption states and lessen the plausibility of dose-dumping. Most of the dosage forms used were reported to be of single unit dosage forms such as tablets and capsules. Whereas, multiple unit buoyant systems include mini tablets or pellets. Multiple unit FDDS is thought to have numerous advantages over single unit systems. However, a literature survey has shown the difference in behavior of single-unit and multiple-unit to be controversial (16).

In order to consider a formulation suited for FDDS, it should have an effective retention time inside the stomach to perform the necessary clinical demands, minimum expected side effects, no effect over the gastric motility, must control the drug release system with a sufficient drug loading capacity and have full degradation and evacuation once the system drug release is over (17). Most of the drug studies for this system have not been able to pass academic and industrial research groups. There are quite a lot of drugs that fit the profile described for FDDS systems, yet so few dosage forms are found in the market. Various types of GRDDS have been reported in literature. The most common GRDDS used are floating and mucoadhesive systems. Possible drug candidates that have been studied over the years are shown in Table 1.

Both in-vitro and in-vivo methods could be used as evaluation parameters of FDDS (18).

In-vitro method:

-Floating capabilities (resultant weight test)

-Content uniformity, hardness, friability (tablets), size and shape

-Dissolution study

-Floating time and floating lag time

In-vivo method:

-Gamma-Scintigraphy

-Gastroscopy

-Ultrasonography

-X-Ray method

3.1. Drug Candidates for FDDS

Drugs, situations and environments that are unsuitable candidates for FDDS include (19,20):

Drugs that have delimited acid solubility (Phenytoin).

Drugs that demonstrate unstable characteristics in gastric environment (Erythromycin, Rabeprazole).

Drugs that are used for selective release in the colon (corticosteroids and 5-amino salicylic acid).

Drugs that cause elevated gastrointestinal irritation.

Unpredictable adherence due to the state of consistent renewal of mucus wall of the stomach.

Fluctuating digestive state of the stomach.

Longer swelling time of hydrogel-based system depending on the excipient.

Size increasing drug delivery systems that may cause possible threat of permanent retention in the stomach following administration.

Super-porous systems showing drawbacks (problems associated with efficient hydrolysable and biodegradable polymer storage).

Table 1. Drugs reported to be used or studied in the formulation of gastroretentive dosage forms.

Drug	Dosage Forms	Half Life (hours)	Drug Category	Ref no.
Acetaminophen	Tablets	2-3	Analgesic and Antipyretic	21
Acyclovir	Tablets	2.5-3.3	Antiviral	21
Acetylsalicylic acid	Tablets, Microspheres	3.1-3.2	NSAID	12,21
Albendazole	Films	8-12	Benzimidazole	12
Alfuzosin	Tablets	3-5	Alpha Blockers	22
Ampicillin	Tablets	0.7-1.5	Beta-Lactam Antibiotic	21
Amoxicillin	Tablets, Microspheres	1	Antibiotic	21,23
Atenolol	Tablets	4	Beta Adrenergic Blockers, Antihypertensive	21
Balofloxacin	Tablets	7-8	Fluoroquinolone Antibiotic	24
Benserazide	Capsules	1.5	DOPA Decarboxylase İnhibitor	21
Captopril	Tablets	2	Antihypertensive- ACE inhibitors	21
Capecitabine	Tablets	1	Anti-Cancer	25
Cefuroxime	Tablets	1-1.5	Cephalosporing Antibiotics	9
Celiprolol HCl	Capsules	5-6	Adrenoreceptor Antagonist	12
Cephalexin	Tablets	0.9	Cephalosporin Antibiotics	12
Chlordiazepoxide	Capsules	5-30	Antipsychotic	21
Chlorpheniramine maleate	Tablets, Microspheres	12-43	Antihistamines	21
Cholestyramine	Microspheres	1	Bile Acid Sequestrants	12
Cinnarizine	Tablets, Granules, Films	3-4	Anti-Histamine and Calcium Channel Blocker	12,21
Ciprofloxacin	Tablets	4-6	First Generation Fluroquinolone Antibiotic	21
Curcumin β-cyclodextrin complex	Beads	-	Antiangiogenic and Antiinflammatory	12
Diazepam	Capsule	1	Benzodiazepines	21
Diclofenac sodium	Granules	2	NSAID	21
Diltiazem	Tablets, Granules, Beads	3-4.5	Calcium Channel Blocker	12, 21
Dipyridamole	Microspheres	α phase 40 mins β phase 10 hours	Antiplatelet	12
Domperidone	Tablets	7.5	Antiemetic	26
Ethoxybenzamide	Microspheres	-	Analgesic and Antiinflammatory	27

Table 1. Continue.

Fluorouracil	Tablets, Granules	16 mins	Anti-Cancer	12,21
Flurbiprofen	Microspheres	6-10	NSAID	12
Furosemide	Tablets, Capsules,	2	Diuretics	12,21
Griseofulvin	Microspheres	9-21	Anti-fungal Agents	21
İbuprofen	Microspheres	2-4	NSAID	21
Indomethacin	Granules, Microspheres	4.5	NSAID	12, 21
Isosorbide dinitrate	Tablets, Granules	5	Nitrates	12,21
İsosorbide mononitrate	Tablets, Granules,	5.1	Nitrates	12, 21
Ketoprofen	Microspheres	2.4	NSAID	21
Lafutidine	Tablets, Microspheres, Films	2	Histamine H2-Receptor Antagonist	28,29,30
L-DOPA	Capsules	1.5	Central Nervous System Agents	21
Levofloxacin	Tablets	6-8	Antibiotic	11
Loratadine	Beads	8.4	Antihistamines	12
Losartan	Tablets	2	Angiotensin receptor blockers	12
Metformin	Microspheres	2-6	Biguanides Antidiabetic	12
Misoprostol	Capsules, Tablets	20-40 (mins)	Anti-Ulcer	12,21
Nicardipine	Capsules, Microspheres	8.6	Calcium Channel Blocker	12,21
Nifedipine	Microspheres	2	Calcium Channel Blocker	12
Nimodipine	Tablets	8-9	Calcium Channel Blockers	21
Ofloxacin	Tablets	8-9	Antibiotic	21,31
Orlistat	Microspheres	1-2	Lipase Inhibitors	12
p-aminobenzoic acid (PABA)	Tablets, Films	53 mins	Aminobenzoic Acids	12,21
Pentoxifylline	Tablets	0.4-0.8	Hemorrheologic agents	12
Piretanide	Tablets, Films	1-1.5	Loop Diuretics	12,21
Piroxicam	Microspheres	50	NSAID	12
Prednisolone	Granules, Films	2-3	Corticosteroids	12,21
Propranolol	Tablets, Capsules	4-5	Antihypertensive	12,21
P-Nitroaniline	Microspheres	1	-	21
Ramipril	Tablets, Beads	2-4	ACE inhibitor	32,33
Ranitidine	Beads	2.5-3	Histamine H2-receptor antagonist, Anti-Ulcer	12
Ranolazine	Tablets	7	Antianginals	34
Riboflavin	Tablets, Powders, Microspheres	1.1	Vitamin	12,21
Rosiglitazone maleate	Microspheres	3-4	Antidiabetic	12

Table 1. Continue.

Sotalol	Tablets, Powders	12	Antiarrhythmics	12,21
Tacrine	Microspheres	2-4	Cholinesterase Inhibitors	27
Tenoxicam	Microspheres	72	NSAIDs	27
Terfenadine	Microspheres	8.5	Histamine H1-Receptor Antagonist	21
Theophylline	Powders, Microspheres	30	Used to Treat Lung Diseases	12,21
Tranilast	Microspheres	5	Antiallergic	21
Ursodeoxycholic acid	Capsules	3.5-5.8 (days)	Anticholelithic	21
Venlafaxine	Tablets	5	Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)	35
Verapamil	Tablets, Microspheres	6	Calcium Channel Blocker, Antihypertensive	12,21
Zidovudine	Tablets	1.1 (Adults)	Nucleoside Reverse Transcriptase Inhibitors-NRTIs, Anti-viral	12

Drugs and environments that are suitable candidates for FDDS include (2,17,20):

Drugs that are active locally in the stomach (e.g. antacid, anti-ulcer drugs, Metronidazole, Levofloxacin).

Helicobacter pylorus (H. pylori) treatment drugs (e.g. Misoprostol, Amoxicillin).

Drugs with limited absorption window in the stomach or upper gastrointestinal tract (e.g. Atenolol, Repaglindine, Para-aminobenzoic acid, L-DOPA, Methotrexate, Levodopa, Riboflavin, Cyclosporine, Furosemide).

Drugs that have changeable properties in the intestinal or colonic environment (e.g. Metronidazole, Captopril, Metformin HCI, Ranitidine HCI).

Drugs that imbalances the pre-existing colonic microbes (e.g. H. Pylori antibiotics such as Amoxicillin, Clarithromycin).

Drugs that are weak basics having low solubility at elevated pH values (e.g. Chlordiazepoxide, Cinnarizine, Diazepam, Cefpodoxime, Verapamil HCI, Furosemide).

Drugs with plasma fluctuations for urinary tract, respiratory and gastrointestinal infections (e.g. Ciprofloxacin).

Drugs that have inadequate absorption from lower GIT (e.g. Atenolol, Lafutidine).

Drugs that are used for specific antibiotics (for H. pylori treatment), antiviral products (HIV, hepatitis), CNS drugs (Parkinson disease, Alzheimer, epilepsy), antihypertensive drugs, antidiabetic agents for type-2 diabetes.

3.2. Advantages of FDDS (3,17,19,20,36)

Possible reduction in dosing and improved patient compliance thanks to ease of administration.

Economic use of dosage forms.

Drugs that are absorbed through the stomach are advantageous (e.g. antacids).

Achieves microbiological and chemical stability compared to other oral routes.

Enhanced activity span for short half-life drugs.

Enhanced bioavailability and therapeutic efficacy of the drugs.

Reduction of intra- and inter- subject variability in plasma drug levels.

Increased pH solubility of drugs.

Fewer side effects and optimised therapy.

Improved selectivity in receptor activation.

Accommodates site specific drug delivery systems.

Advantageous in case of dynamic intestinal mo-

vements. Keeps the drug in buoyant conditions inside the stomach to get an enhanced response.

Amplifies the pharmacological effects and enhances the clinical performances by reducing the drug concentration fluctuations over a critical concentration.

3.3. Disadvantages of FDDS (3,17,19,20,36)

Not practicable for drugs that have stability or solubility problem in the upper gastrointestinal tract.

Some drugs arranged for the buoyant system may cause irritation and lesions to gastric mucosa.

Heightened fluid levels are essential inside the stomach for the drug to float sufficiently.

Difficulty estimating the detailed motility of the stomach.

Swelling system should be rapid acting once the drug reaches the stomach.

Swallowing complications with children or in case of unconscious patients.

Capability of the drug system to float relies immensely in the hydration state of the dosage form.

Since the mucus present on the stomach wall is in a state of continuous renewal, the adherence is inconstant.

3.4. Use of FDDS in Helicobacter Pylorus

Helicobacter pylorus (H. pylori) is one of the leading diseases of stomach lining and has been recognised worldwide to be a major pathogen that lives in the gastric environment. It is very likely that half the world's population has been colonised (7). H. pylori is a causative organism that causes a persistent infection. The eradication treatment lasts for weeks at a time. Common therapy choices always include at least two antibiotics plus an acid suppressing agent. Even though these triple therapies are proven to be effective, some reports and clinical trials suggest ineffective treatment in some cases. Quadruple therapy is becoming popular due to an increase in the resistance of standard triple therapy (3). It is effortful to annihilate these bacteria from the human body. Reasons for ineffective treatment could be due to a limited residence time of antimicrobial agents in the stomach or degradation of the antibiotics in gastric acid. Researchers have studied new formulated approaches and have given consideration to FDDS. One approach is using mucoadhesive microspheres. This idea was first introduced due to their ability to adhere to the mucus layer. The system then releases the drug in a sustained manner. Absorption of an antibiotic into the mucus through the mucus layer is thought to be an effective H. pylori treatment when compared to absorption through blood. There are many ongoing studies around antibiotics as floating dosage forms, and one has even made it onto the market (Clarithromycin) (13,23,36).

4. Factors Affecting Gastric Retention

There are numerous factors affecting the GRT and floating ability of the drug. For oral dosage forms, a large volume of water is administered while taking the medicine which increases the pH of the stomach content. Increased acidity, volume, viscosity and meals content are the main factors affecting the gastric emptying rate. In the digestive phase, tablets with large sizes are emptied during the housekeeping waves, while smaller sized tablets easily depart the stomach. Some of the important factors affecting the gastric retention are given below (3, 5,17,37).

Density: The density of the drug system directly affects the gastric emptying rate. When compared, it should be less than the gastric content of the stomach (1.004 g/ml). The density of the drug determines the area it will take in the stomach. If the density of the system is lower than gastric content it will float to the surface and sink to the bottom if the system has a higher density than the stomach content. The drug that is buoyant in the gastric juice is released slowly with a desired rate from the system.

Size and shape: The diameter of the dosage unit is crucial as a formulation parameter. It was described that the dosage form unit with a diameter of more than 7.5 mm has an increased gastric residence time compared to those with a diameter of 9.9 mm. The dosage form with a tetrahedron conformation or a ring shape devices with a flexural modulus of 48 and

22 kiloponds per square inch are reported to have improved GIT for 90-100% retention at 24 hours when compared with other aspects of the particles. As the size of the dosage form increases, so does the gastric retention time.

Fed state or unfed state: Generally the existence of food augments the gastric retention time of the dosage from in the gastrointestinal tract. During fasting conditions, the GI motility is characterised by the MMC that occurs every 1.5-2 hours or periods of capable motor activity. The MMC sweeps undigested material from the stomach. If the timing of the administration of the formulation coincides with that of the MMC, the GRT of the unit is expected to shorten. But in a fed state, the MMC is delayed and the GRT is substantially longer.

Nature of the meal: Consuming indigestible polymers of fatty acid salts can change the motility cycle of the stomach to a fed state. This decreases the gastric emptying rate and prolongs the drug release.

Caloric content: GRT can be expanded between 4-10 hours after a meal consisting of high proteins and fats is consumed. An increase in caloric content slows down gastric emptying time.

Frequency of feed: The GRT can increase by over 400 minutes when proper meals are given, compared with a single meal due to the low frequency of MMC.

Gender: Normally, the gastric emptying rate is slower in females than males. Mean ambulatory GRT in meals (3.4±0.4 hours) is less when compared with age and race-matched female counterparts (4.6 ±1.2 hours), regardless of the weight, height and body surface.

Age: Elders have a significantly longer GRT, in particular those over 70 years of age.

Posture: GRT can vary between supine and upright ambulatory positions of the patients.

Single or multiple unit formulation: Multiple unit formulations are more applicable than single unit dosage forms and allow a larger margin of safety against dosage form deficiency and co-administration of units with different release profiles.

Miscellaneous: Biological factors effect gastric emptying.

Concomitant drug administration: Some drugs can alter the floating time of the system when taken together. Examples include metoclopramide, codeine, cisapride and anticholinergics like propantheline and atropine.

5. Classification Of GRDDS

Various approaches were studied for preparing gastroretentive drug delivery system. These systems have a common goal, to keep the drug system for longer periods in the stomach. Thanks to comprehensive research, we now understand the process of gastrointestinal transit in human's, contrary to before. Thus, capable of designing a better system for drug delivery. GRDDS techniques include floating systems, expandable systems, swellable systems, mucoadhesive systems, high-density systems, magnetic systems, raft systems, and super-porous hydrogel. Among all these, the floating dosage form has been used most commonly. Other techniques which are non-floating systems, are able to remain in the stomach for an extended time and do not float on the content of the stomach. Floating dosage forms are divided into 3 groups: raft forming systems, effervescent systems, non-effervescent systems. Another method of classification of GRDDS could depend on two main factors: small-size particles that have bioadhesive properties including propensity to float on the stomach content or; larger swelling objects that will be retained in the stomach due to their size. The method of classification depends on the approach to be taken (11). In Figure 2, systems have been classified according to their floating ability in the gastric content.

5.1. Non-Floating Drug Delivery Systems

5.1.1. Mucoadhesive or Bioadhesive Systems

The mucoadhesive system was first introduced by Park and Robinson. This is a complex system with several mechanisms. The mucoadhesive systems are capable of extending the GRT by adhering them to the gastric mucous membrane. This approach uses bioadhesive polymers. These polymers can adhere to the epithelial surface in the stomach. Gastric reten-

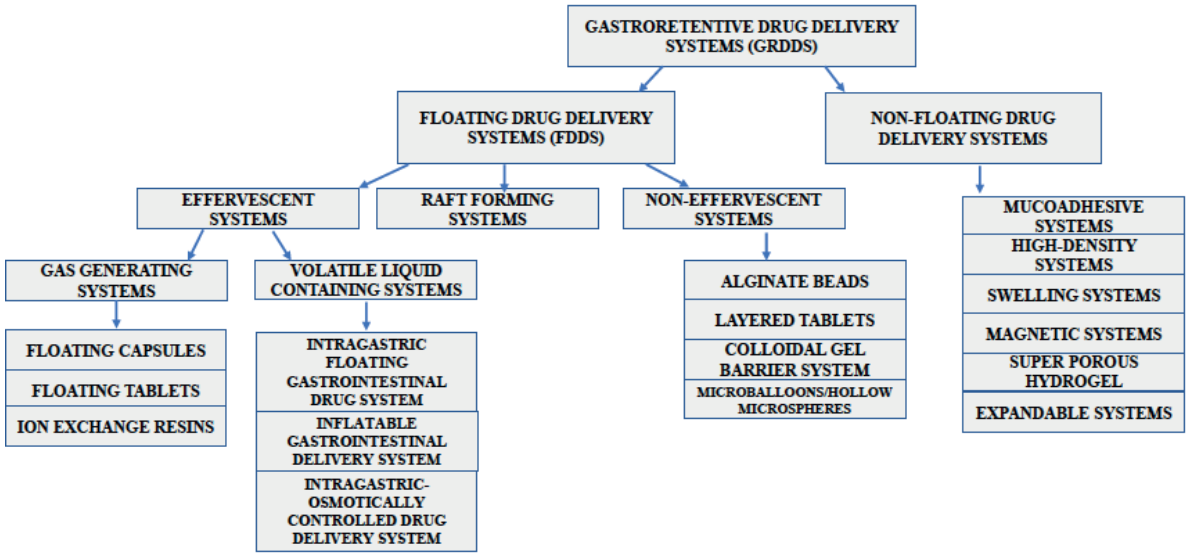

Figure 2. Classification of Gastroretentive Drug Delivery Systems (12).

tion is extended by increasing the affinity and duration of contact between gastroretentive drug delivery system. The interaction between a positively charged polymer and negatively charged mucosal surface might ease the bioadhesive process (2).

Excipients that have been used are polycarbophil, carbopol, chitosan, lectins, alginate and gliadin etc. Due to the formation of inter and intra chain disulphide bonds, these conjugates have the ability to strongly enhance cohesive properties which results in an almost zero order release of the model drug (2). The adhesion of used polymers in the formulation with the mucous membrane may be mediated by hydration, bonding, or receptor mediated.

Hydration mediated adhesion: Hydrophilic polymers become clingy and mucoadhesive upon hydration.

Bonding mediated adhesion: May involve mechanical or chemical bonding.

Receptor mediated adhesion: Takes place between certain polymers and specific receptors that are defined on gastric cells (17).

The dosage forms that are orally taken will adhere to the gastric epithelial cell surface or mucin, then enhance the intimacy and continuance of contact of biological membrane and the drug. Thus, the gastric residence time will be extended. One way to overcome limitations seen with this system could be done by developing the floating systems paired with mucoadhesion characteristics. This will improve the adherence of the dosage form to the mucous lining of the stomach wall (7,12,17). This system appeals to researches due to efficient responses accomplished through formulations. It is one of the approaches that is most concentrated on for FDDS.

5.1.2. High-Density Systems

These systems are prepared so that the drug system lodges in the rugae of the stomach and copes with the peristaltic movements. Systems are expected to retain in the lower part of the stomach when the density is 1.3 g/ml or higher. Heavy pellets are assumed to be positioned in the lower part of the antrum corresponding to their higher density. The pellets have an increased gastric residence time both in fasted and fed state when the density is at least 1.5 g/ml (17).

5.1.3. Swelling Systems

After oral administration, these systems extend to a point where the drug delivery system inhibits their passage through the pylorus. Thus, the dosage form remains persistent in the stomach for an exten-

ded period of time. These systems are sometimes referred to as 'plug type' systems due to their ability to remain lodged at the pyloric sphincter (Figure 3). Choosing a suitable polymer is essential in order to obtain the correct molecular weight and swelling characteristics. The polymers used in this system is generally biodegradable. The polymer in the system takes within the water and swelling occurs due to the interaction that occurs between the polymer and gastric fluid. In order to achieve patient compliance, the drug taken should be small enough to swallow easily (38,39).

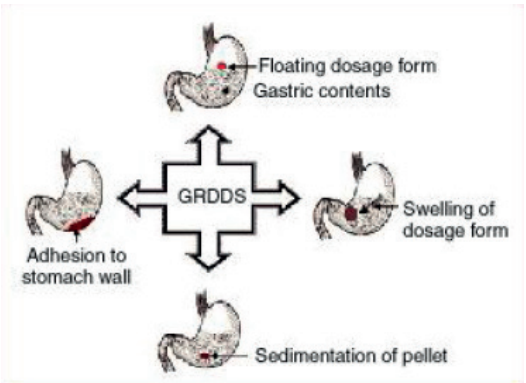

Figure 3. Illustration of gastroretentive drug delivery systems (40).

5.1.4. Magnetic Systems

These systems are another alternative approach to improve the gastric retention time. The methods used here are facile. There are two magnets used, one within the dosage form which is a small internal magnet and the other placed outside on the abdomen over a specific position. The later magnet is extracorporeal. The position of the external magnet is the main aspect in this system. The incorrect precision of the magnets position may compromise the assent of the patient (41). This system could be considered as the lesser practical alternative.

5.1.5. Super-Porous Hydrogel

The system here has hydrogels that are designed by multiple approaches such as phase division, gas-blowing method, cross-linking method, etc. The system here swells up to 100 times its original size by capillary wetting through various pores (2). The gas-blowing method is the most common engaged method for formation. Homogenous porous hydrogels are super-porous hydrogels. The formation of the system takes place by synchronised gelation and foaming processes. In order to become a gastric retention device, hydrogels should have the following characteristics (39):

-The size of the system out of the package should be agreeable for easy swallowing.

-Fast swelling following administration that is sufficient to overcome gastric emptying by IMMC.

-The sizes of swollen hydrogels should be large enough to be kept in the stomach.

-Strong swollen hydrogels to endure contraction pressure, abrasion and shear forces in stomach.

5.1.6. Expandable Systems

This system was first designed for possible veterinary use. Later the design was adapted and studied for enhanced drug therapy in humans (4). The dosage form that arrives in the stomach will withstand gastric transit as long as the system is larger than the pyloric sphincter. The dosage form should be small enough to swallow but at the same time must not cause any gastric blockage. Once the drug is taken, it will greatly increase in size due to unfolding or swelling processes that take place in the stomach. Swelling usually occurs due to diffusion. The mechanism here is for the system to swell and extend to a point in which the exit of the drug from the pylorus is avoided. As a result, the drug is retained in the stomach for an extended time. After the drug is released, their dimensions are minimised to be discharged from the stomach. Also, if the sizes of these systems expand over 12-18 mm approximately, they exhibit the inclination to remain logged at the pyloric sphincter. When polymeric matrices are used in the formulation, the system remains in the gastric cavity for several hours. This occurs even when the stomach is in the fed state. Three required configurations are essential for the system: a small configuration for oral administration, an expanded gastro-

retentive form and a final small form that allows evacuation after the drug gets released (7, 42).

5.2. Floating Drug Delivery Systems (FDDS)

5.2.1. Effervescent Floating Dosage Forms

These are matrix type of systems that are fixed with the aid of swellable polymers. The formulation here is prepared in a way that once the drug arrives in the gastric content, carbon dioxide is released and gets entrapped in swollen hydrocolloid. An upward motion takes place. This mechanism is what provides the floating ability to the system (43).

Effervescent systems can be classified into two types:

-Volatile liquid/vacuum systems

-Gas generating systems

5.2.1.1. Volatile Liquid Containing Systems

The system here uses devices that are osmotically directed by floating systems. Inflatable chambers are used in order to extend the gastric residence time of the drug. The chambers hold a liquid such as ether or cyclopentane. The liquid found here gets converted to a gaseous state at body temperature and causes the expansion of the system. A hollow defaced unit is found which can be transitioned from a collapsed to an expanded position and then returned back to a collapsed position following a prolonged period of time. The defaced unit is made of 2 chambers that are separated by moveable, pressure responsive and impassable bladder. The device here inflates and releases the drugs over an incessant process from the reservoir into the gastric fluid. Also, this device contains a bio-erodible plug that is made up of PVA, Polyethylene, etc. (3,41).

5.2.1.2. Gas Generating Systems

The system used here is based on low density characteristics and the formation of carbon dioxide within the device after the drug comes in contact with body fluids. The formulation contains excipients such as citric/tartaric acid and carbonate/bicarbonate salts to release carbon dioxide. Once the drug arrives in the stomach, carbon dioxide gets released by the acidity of the gastric content and is entrapped inside the jellified hydrocolloid. An upward motion of the dosage form takes place in the stomach content and causes floating (43). Swellable polymers that could be used are such as methocel, polysaccharides, and effervescent components (6).

5.2.1.3. Ion Exchange Resins

A coated ion exchange resin system loaded with bicarbonates and prepared as beads formulation has gastric retentive properties. In this system, a drug that is negatively charged is bound to the resin. In order to overcome the sudden loss of carbon dioxide, the beads are encapsulated in a semi-permeable membrane. Once the drug arrives at the gastric content, an exchange of bicarbonate and chloride ions occurs in the acidic environment. While uncoated beads would sink to the bottom quickly, a floating layer of resin beads is carried to the top of the gastric content (7). This system can be combined with floating delivery or bioadhesive systems (2).

Microparticulates that were studied have demonstrated successful clinical investigations. Pivotal studies performed at Nottingham University, UK, have revealed that the oral dose forms containing finely divided ion-exchange resins can provide uniform distribution within the stomach with prolonged gastric residency (11).

5.2.2. Non-Effervescent Floating Dosage Forms

Another name for non-effervescent systems is hydrodynamically balanced systems (HBS). These systems commonly use polysaccharides, gel-forming highly swellable cellulose type hydrocolloids, and matrix forming polymers (polymethacrylate, polyacrylate, polystyrene, polycarbonate). Following administration, the drug will absorb gastric fluid and swell unconstrainedly (41). Air that gets trapped in the swollen polymer provides the buoyancy to the dosage forms. The diffusion of solvent will be regulated

by the gel structure. This gel barrier is maintained by the hydration of adjacent hydrocolloid layers while the outer surface goes into solution. This results with the drug dissolving and diffusing out with the diffused solvent which then produces a withdrawing boundary of the system. Excipients that are commonly used in these systems are carbopol, sodium alginate, hydroxypropylmethyl cellulose, agar, polyvinyl acetate, and calcium chloride (7, 37).

Different types of non-effervescent system are given below.

5.2.2.1. Alginate Beads

In this system, multi-unit floating dosage forms have been refined from freeze dried calcium alginate. The beads used here are spherical shaped and are approximately 2.5 mm in diameter. These beads can be prepared by dropping the sodium alginate solution into an aqueous solution of calcium chloride. This causes the precipitation of calcium alginate. Afterwards, the beads are separated, snap-frozen in liquid nitrogen. Lastly, these beads are freeze-dried at -40°C for 24 hours. A porous system will be formed that can float over 12 hours in the stomach content (43). The buoyant beads here give an extended residence time of more than 5.5 hours (6).

5.2.2.2. Microballoons/Hollow Microspheres

The system here uses microspheres that are free flowing powders consisting of proteins or synthetic polymers that have a size of less than 200 micrometers. Researchers consider this system to be the most favourable. The drugs here are prepared by a novel emulsion solvent diffusion method and have a hollow space inside. The outer polymer of the system is loaded with drug. The polymer is dissolved in an organic solvent while the drug is either dispersed or dissolved in the polymer solution. The solution that contains the drug is emulsified into an aqueous phase containing polyvinyl alcohol to form oil in water emulsion. Afterwards, a stable emulsion is formed. A continuous stirring or increase in temperature under pressure is used in order to evaporate the organic solvent. Removal of the solvent leads to polymer precipitation at the o/w interface of droplets. This leads to a formed cavity. Finally, the drug is hallowed and has buoyant properties (27,44) (Figure 4).

The promising factor of polymeric microspheres is due to their superior encapsulation and sustained release capabilities. These properties can be managed by their textural and physical appearance. Furthermore, thanks to their structural flexibility, stability, and functionality they are ideal candidates to encapsulate numerous compounds (23). Buoyant microspheres are also effective in delivering insoluble and sparingly soluble drugs. In case the drug in question is a weak basic that is poorly soluble at an alkaline pH, use of hollow microspheres may avoid the chance for solubility to become the rate-limiting step in drug release. The absorption profile of the drug will be altered beneficially, and the bioavailability of the drug will be advanced. Usually, non-steroidal anti-inflammatory drugs have high GIS disadvantages. In this case, the system allows very effective controlled release of such drugs and thus reduces this side effect. Floating microspheres are also considered to be effective for the treatment of duodenal and gastric cancers. Recent developments for hollow microspheres include Eudragit, polystyrene floatable shells, acrylic resins, cellulose acetate, PMAA, polyethylene oxide, Gelucire floating granules and polycarbonate floating balloons. Since floating microspheres are taken up from specific sites of the gastrointestinal mucosa, this leads to the idea that by continuous supply of the drug to its most efficient site of absorption, a more effective form of use of the dosage form

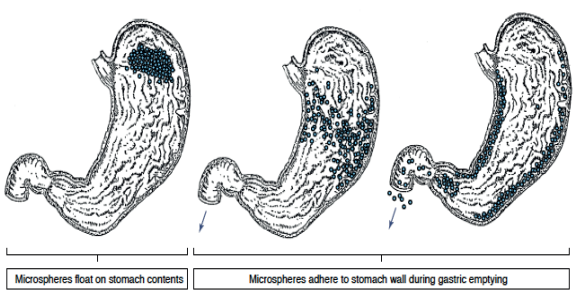

Figure 4. Process of bioadhesive microspheres residing in the stomach fluid (11).

can be found in drugs that are normally not taken orally. Such drugs include low-molecular-weight heparin, calcitonin (protein and peptide drugs), insulin, vasopressin, erythropoietin, and LHRH (27).

5.2.2.3. Layered Tablets

Non-effervescent floating dosage forms contain single-layer floating tablets and bilayer floating tablets. For single-layer, the formulation is a mixture of the drug with gel-forming hydrocolloid. The drug begins to swell when it arrives in the gastric fluid and is able to maintain a bulk density that is lesser than unity. Whereas, bilayer-floating tablets has two layers. First layer causes immediate release which releases initial dose from the system. On the other hand, the other layer sustains released conventional tablets (44).

5.2.2.4. Microporous Compartment System

The technology used in this system is based on the encapsulation of a drug reservoir inside a microporous compartment. This compartment should have pores along its top and bottom walls. The peripheral wall of the given drug reservoir compartment is obstructed completely in order to prevent any direct contact of the undissolved drug with the gastric surface. Once the drug reaches the stomach, the entrapped air inside floatation chamber causes the medicine to float over the gastric content of the stomach. Gastric fluid enters through the aperture and dissolves the drug. The dissolved drug is then taken to the intestine for absorption via constant transport (7,43). Drugs that have been studied for this system include Repaglinide, Diltiazem HCl, Chlorpheniramine maleate, Theophylline HCl, Verapamil HCl, Orlistat (27).

5.2.2.5. Colloidal Gel Barrier System

Sheth and Tossounian were the first to design this HBS (6). The drugs used in this system contain gel-forming hydrocolloids that allows the medicine to remain floating on the gastric content. The hydrocolloid in the system hydrates once it comes in contact with the gastric fluid to form a colloidal gel barrier around its surface. The air that gets trapped by the swollen polymer maintains a density that is less than one. A homogeneous system is usually prepared within a gelatin capsule. Once the drug comes in contact with the gastric fluid, the capsule gets disintegrated very fast and the polymer is hydrated and then floats. Thus, a colloidal gel barrier is formed with a density that is less than 1. Examples for excipients used in this system include: polysaccharides, HPMC, hydroxypropyl cellulose, and matrix-forming polymer (polystyrene, polyacrylate, polycarbophil) (38, 41).

5.2.3. Raft Forming Systems

Also known as in situ gelling techniques, these systems have obtained increased attention over the years. The main area of use includes the delivery of antacids and the delivery of drugs for gastrointestinal infections and disorders. These systems incorporate alginate gels. The mechanism used here includes the formation of viscous cohesive gel when the system comes in contact with gastric fluids, as shown in Figure 5. Here each part of the liquid swells and forms a continuous layer that is called a raft. Raft forming systems have a low bulk density created by the formation of carbon dioxide. This leads to the floatation of raft on gastric fluids. This system is commonly used for gastroesophageal reflux treatment with Liquid Gaviscon (37,39).

According to Choi *et al.* alginate floating beads that contain either CaCO3 or NaHCO3 as gas forming agents have shown different porosity degrees, bed gel strengths and thus have amended floating behaviours. When comparing the two gas forming agents, the later has significantly increased porosity and pore diameter. The incorporation of CaCO3 resulted in smoother beads of higher gel strength than those that were produced with NaHCO3. This shows that CaCO3 is the exceeding gas forming agent in alginate bead formulations (45).

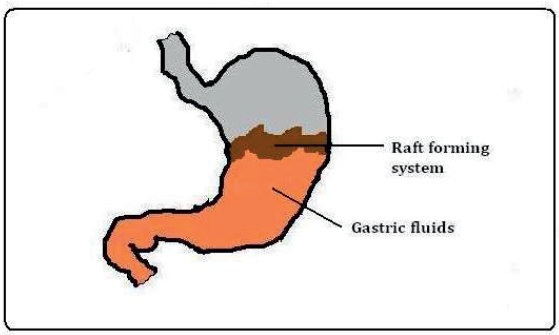

Figure 5. Representation of raft forming systems (37)

6. Excipients Used In Floating Drug Delivery Systems (FDDS)

Excipients used for the formulation are immensely important to determine the characteristics of the drug delivery system. The common aim is generally to achieve a drug formulation that is able to stay in the gastric content for a prolonged time and effectively deliver the content it is carrying. The role of polymers is highly important. Some are more advanced than others, such as Eudragit and chitosan. Other excipients used include pore forming agents (citric acid, silicates), surfactants (sodium lauryl sulfate, poly vinyl alcohol), and gas generating agents (sodium bicarbonate, calcium carbonate) (46). A floating dosage system could also include excipients such as lubricants, glidants, anti-microbial agents, colouring agents, fillers, and binders.

There are quite a few systems that are used for floating dosage forms. These systems could easily be divided into two categories: effervescent and non-effervescent systems. Gas-generating agents are used for effervescent systems. Whereas, swellable polymers or hydrocolloids are used for non-effervescent systems (46). Excipients that are most commonly used in effervescent systems include agar, carbopol, polyacrylate polymer, HPMC, sodium alginate, polycarbonates, polyvinyl acetate, polyethylene oxide and calcium chloride (18). Classification of polymers that are commonly used in floating dosage forms are given in Table 2.

The physicochemical background of the excipients used for the formulation play a crucial role in GRDDS. Especially when determining the density of the system for its floating ability. Correspondingly, viscosity, shape, size and molecular weight of the polymer also affects the dosage form. One example to give would be the use of high swelling excipients such as crospovidone and sodium carboxymethyl cellulose to formulate super porous hydrogel systems. Or in case of expandable system, polymers with high swelling properties are more agreeable (2).

Excipients that are could be added to the formulation of floating dosage forms are given below (18,48):

Buoyancy increasing agents: Used for increasing the floatation of formulation. May be adapted up to 80% by weight.

Hydrocolloids: Synthethics, anionic or non-ionic and modified cellulose derivatives are suitable hydrocolloids and must hydrate in acidic medium. The bulk density should be less than one once they come in contact with the gastric fluid. Examples: acacia, agar, alginates, bentonite, casein, gelatin, pectin, veegum, HEC, MC, Na CMC and HPC.

Table 2. Common excipients used with gastroretentive floating formulations.

Systems	Polymers/Materials Used
Hollow Microspheres	Cellulose Acetate, Chitosan, Eudragit, Acrycoat, Methocel, Polyacrylates, Polyvinyl Acetate, Carbopol, Agar, Polyethylene Oxide, Polycarbonates, Albumin, Gelatine, Starch (21).
Mucoadhesive	Carbopol, Hydroxypropyl Methylcellulose, Chitosan, Polycarbophil, Carbopol, Lectins, Carboxy Methyl Cellulose, Gliadin, Polyethylene Glycol, Tragacanth, Dextrin, Chitosan, Sodium Alginate, Cholestyramine, Poly Acrylic Acid, Sucralfate (2).
Super-Porous Hydrogel	Crospovidone And Sodium Carboxymethylcellulose (2).
Effervescent Systems	Agar, Carbopol, Hydroxypropyl Methyl Cellulose, Polyacrylate Polymer, Polyvinyl Acetate, Sodium Alginate, Calcium Chloride, Polyethylene Oxide, Polycarbonates (18).
Non-Effervescent Systems	Hydroxypropyl Methyl Cellulose, Ethylcellulose, Hydroxypropylcellulose, Carrageen, Polyvinyl Acetate, Carbopol, Sodium Alginate, Agar, Calcium Chloride (7,37,21).
Swelling Systems	Acacia, Pectin, Chitosan, Agar, Casein, Bentonite, Veegum, Hydroxypropyl Methyl Cellulose, Gellan Gum, Sodium Carboxy Methyl Cellulose, Methyl Cellulose, Hydroxy Propyl Cellulose (7).
Colloidal Gel Barrier System	Hydroxy Propyl Cellulose, Polysaccharides, Matrix-Forming Polymer (Polycarbophil, Polyacrylate, Polystyrene) (7,41).
Raft Forming System	Hydroxy Propyl Cellulose, Xanthan Gum, Cellulose Derivatives, Alginate Sodium, Carbopol (47).

Inert fatty materials: These are digestible pharmaceutical inert fatty materials that have a specific gravity less than one and can be added to the formulation in order to increase the buoyancy of the system. Examples: purified grades of beeswax, fatty acids, glycerides, long chain alcohols, and mineral oils.

Release rate accelerant: Used in order to modify the release rate of the medicament from the formulation. These may be present from about 5-60% by weight. Examples: lactose, mannitol.

Release rate retardant: Used in order to decrease the solubility and extend the release of medicament from the formulation. Examples: insoluble substances such as talc, magnesium stearate and dicalcium phosphate.

Miscellaneous: Pharmaceutically admissible adjuvants that can be incorporated in the dosage forms when required. They do not adversely affect the hydrodynamic balance of the system. Examples: stabilisers, preservatives, lubricants.

6.1. Polymers Used in Floating Drug Delivery Systems

The use of polymers has become a popular choice in dosage forms these past few decades thanks to their wide range of application. The characteristics of each polymer greatly effects the quality of the dosage form. A polymer could be nonionic, cationic or anionic (2). The use of a suitable polymer is especially important when designing floating drug delivery systems. For example; mucoadhesive polymers, given in Table 3, could be the first line of choice when determining suitable formulations. Polymers could be used according to their behaviour. When categorising them, we focus on the basis of their origin (23,46):

-Natural polymers (pectin, starch, chitosan, sodium alginate).

-Semi-synthetic polymers (chitosan derivatives, HPMC, EC).

-Synthetic polymers (lactic acid derivatives, acrylic acid derivatives)

The most commonly used gel-forming or highly swellable polymers are those with cellulose type hydrocolloids. These are polysaccharides, and matrix-forming polymers (polymethacrylate polycarbonate, polyacrylate, polystyrene) (45). The amount of polymer used for the formulation of drug delivery should be balanced. If the polymer used is too much, then the system will not be able to effectively distribute the drug. And if the amount is too little, the system will not float. Table 4 shows polymers that are used in floating dosage forms.

Another approach would be choosing mucoadhesive polymers. There are two types of mucoadhesive polymers available: water soluble, water-insolub-

Table 3. Mucoadhesive polymers (4).

Natural	Synthetic	Biocompatible	Biodegradable
Sodium alginate	Polyvinyl alcohol	Esters of hyaluronic acid	Poly(lactides)
Pectin	Polyamides	Polyvinyl acetate	Poly(glycolides)
Tragacanth	Polycarbonates	Ethylene glycol	Poly(lactide-coglycolides)
Gelatin	Polyalkylene glycols		Polycaprolactones
Carrageenan	Polyvinyl ethers		Polyalkyl-cyanoacrylates
Guar gum	Polymethacrylic acid		Polyorthoesters
Chitosan	Polymethyl-methacrylic acid		Polyphosphoesters
Okra gum	Methylcellulose		Polyanhydrides
Gellan gum	Ethlcellulose		Polyphosphazenes
	Hydroxypropyl-cellulose		Chitosan
	Hydroxypropyl-methylcellulose		Polyethylene oxide
	Sodium-carboxymethyl cellulose		

Table 4. Polymers used in floating dosage forms (39).

Natural Polymers	Synthetic Polymers
Alginates	Carbopol 934 P
Aloe Mucilage	Eudragit (RL100, L100, RS PO, RS EPO, S100)
Arabinogalactose	Ethyl Cellulose
Carrageenan	HPMC K4M
Chitosan	HPMC K15M
Gellan Gum	HPMC K100M
Guar Gum	Hydroxyethylcellulose
Honey Locust Gum	Hydroxypropyl Cellulose
Karaya Gum	Methylcellulose
Okra Gum	Polyalkylene Glycols
Pectin	Polyamides
Psyllium Husk	Polycarbonates
Starch	Polyvinyl Alcohol
Tamarind Gum	Polyvinyl Ethers
Tara Gum	Polyvinylpyrrolidone (PVP)
Xanthan Gum	Sodium Carboxy Methyl Cellulose

le polymers with swellable networks. An appropriate polymer should be nontoxic, non-irritant, inert, adhere quickly to most tissues, possess site specificity and form strong non-covalent that binds with the mucin epithelial cell surface (8). Carbopol and HPMC are two polymers used in mucoadhesive systems for their high mucoadhesion strength (2). Another one would be chitosan. The polymer chitosan is known to bind well to mucus. Animal studies have also shown that the microparticles coated with chitosan adhere well in the intestine of animals. However, this does not directly mean that the administered drug will have good bioavailability. The incorporated drug must be released at an appropriate rate and be firm in the lumen to have a chance of absorption (11).

7. Studies on Floating Dosage Forms

In the past three decades, researchers have dedicated their attention to perfecting oral drug delivery systems by using floating dosage forms. Classic or innovative approaches have been studied for different drugs. A few have even made it to the market (Table 5). Research in this area has especially focused on acid-surpassing agents. Some of the promising new studies of the past few years has been mentioned below.

A study was done by Shaik and *et al.* for capecitabine as floating tablet dosage forms for treating stomach cancer in order to decrease frequency of administration to once daily. An orally taken anti-cancer drug is usually preferred by the patient. Capecitabine (CPC) is a tumour activating oral prodrug of 5-FU that improves safety and efficacy. Floating tablets were prepared using direct compression method. HPMC K15M, HPMC K4M, HPMC LVCR 1000 and partially pre gelatinised starch was used in order to prepare different formulations and to find the best concentration (25).

Alexander and *et al.* (34) aimed to design and evaluate floating types of gastroretentive dosage forms of Ranolozine using hydrophilic polymers such as Xanthan, HPMC K100M, HPMC K4M and Guar Gum. All four polymers were of good quality. In each case, the necessary requirements for gastroretentive dosage forms was fulfilled. The effect of different formulation parameters such as swellable polymer on floating properties and concentration of effervescent agent and drug release kinetics were studied and formulations used were optimised.

Gong and *et al.* (22) developed a research in order to formulate a multiple-unit floating mini-tablets and to evaluate the possibility of using these mini-tablets as a delivery system to improve the drug absorption for drugs with a narrow absorption window. Excipients used included HPMC K100M and Carbopol 971P as release retarding agents and sodium bicarbonate (NaHCO3) as a gas-forming agent. The floating characteristic parameters and *in vitro* release of formulations were evaluated. Also, in vivo pharmacokinetic studies in rabbits were performed in order to optimise the formulation. Results illustrated that the gastric floating mini tablets could be a promising approach to developing a drug delivery system for drugs with a narrow absorption window.

A study was done by Arvapally and *et al.* (24) in order to develop and evaluate gastroretentive drug delivery system of fluoroquinolone antibiotics, Balofloxacin. The objective here was to obtain site-specific drug delivery and to extend the duration of

Table 5. Commercial Products of Gastroretentive Drug Delivery Systems (5,18,38,44).

Product	Active Ingredient	Remarks/Technology	Indication	Company
Accordion Pill TM	-	Expandable film filled in capsule	-	Intec, Pharma
Amalgate Float Coat	Aluminum-magnesium antacid	Floating dosage form	Antacid	-
Baclofen GRS	Baclofen	Coated multi-layer floating and swelling system	Muscle relaxant	Sun Pharma, India
Cafeclor LP	Cefaclor	Minextab Floating	Antibiotic	Galenix, France
Cifran OD	Ciprofloxacin	Effervescent floating form	Antibiotic	Ranbaxy, India
Cipro XR	Ciprofloxacin hydrochloride	Erodible matrix based system	Antibiotic	Bayer, USA
Conviron	Ferrous sulphate	Colloidal gel forming FDDS	Iron supplement	Ranbaxy, India
Coreg CR	Carvedilol	Gastro retention with osmotic system	Anti-hypertension and Congestive heart failure (Beta-Blockers)	Glaxosmithkline
Cytotec	Misoprostol	Bilayer floating capsule	Anti-Ulcer	Pharmacia Limited, UK
Gabapentin GR	Gabapentin	Polymer based swelling technology	Anticonvulsants	Depomed, USA
Glumetza	Metformine HCI	Polymer based swelling technology	Antidiabetic	Depomed, USA
Inon Ace Tablets	Simethicone	Foam based floating system	Antacid	Sato Pharma, Japan
Kadian	Morphine sulfate	-	Pain relief	Sumitomo Pharma, Japan
Liquid gaviscon	Alginic acid and Sodium bicarbonate	Effervescent floating liquid alginate preparation	Antacid	Reckitt Benckiser Healthcare, UK
Madopar	Levodopa and Benserzide	Floating, CR capsule	Anti-Parkinson's	Roche, UK
Metformin HCl LP	Metformin HCl	Minextab Floating	Antidiabetic	Galenix, France
Metformin GR	Metformine HCl	Polymer based swelling technology	Antidiabetic	Depomed, USA
Oflin OD	Ofloxacin	Gas-generating floating tablets	Antibiotic	
Prazopress XL	Prazosin HCl	Effervescent and swelling-based floating system	Anti-hypertension	Sun Pharma, Japan
ProQuin XR	Ciprofloxacin	Polymer based swelling technology	Antibiotic	Depomed, USA
Riomet OD	Metformine HCl	Effervescent floating system	Antidiabetic	Ranbaxy, India
Topalkan	Aluminum magnesium antacid	Floating liquid alginate	Antacids	Pierre Fabre Medicament, France
Tramadol LP	Tramadol	Minextab Floating	Pain relief	Galenix, France
Valrelease	Diazepam	Floating capsule	Anti-Parkinson's	Roche, UK
Xifaxan	Rifaximin	Bioadhesive Tablets	Antibiotic	Lupin, India
Zanocin OD	Ofloxacin	Effervescent floating system	Antibiotic	Ranbaxy, India

action of the drug. Materials used to formulate included HPMC K4M, HPMC K100M, xanthan gum, microcrystalline cellulose as swelling agent and gas generating agent like sodium bicarbonate. All the formulations that were prepared were evaluated for floating properties, swelling characteristics and drug release studies. The floating lag times were found to significantly increase with the increasing concentration of the polymers. After dissolution study of prepared balofloxacin floating effervescent tablets, the conclusion was that HPMC K100 and xanthan gum showed better control at release effect.

A study was carried out in Turkey by Senyigit and *et al.* (49) in which they developed and evaluated gastroretentive particulate delivery systems using Riboflavin-5'-monophosphate sodium salt dihydrate as a model drug. In this study, polyacrylic acid-cysteine and chitosan-4-thiobuthylamidine were evaluated and compared as anionic and cationic polymers. *In vitro* release studies, mucoadhesion studies, and evaluation of swelling behaviour was done. It was deduced that drug loading polyacrylic acid particles were significantly higher than chitosan particles. Also, the release of the drug studied from the thiolated particles was slower compared with unmodified particles. Thiolated particles, both anionic and cationic, prepared by air jet milling were shown to have improved mucoadhesive and drug-controlled release properties.

Kucukoflaz and *et al.* (50) performed a study where they synthesised polymeric microspheres in order to be used in drug delivery systems. The aim here was to determine the micromechanical properties of drug release applications by nano indentation. Compressive elastic moduli of individual microspheres determined by atomic force microscopy and force spectroscopy was reported. It was shown that vinyl acetate was effective with the swellability of the material used with the formulation. As the elastic modulus got reduced, the uniformity was increased. Also, it was believed that the copolymer that had increased vinyl acetate content could carry drugs with high solubility in aqueous phase. The method used in this study was believed to be a safe, reliable and basic method when determining whether microspheres affect individual micromachining properties.

CONCLUSION

Oral dosage delivery forms face many challenges in the pharmaceutical industry. Especially when the drug in question is absorbed in the upper part of the gastrointestinal system. Due to this, the concept of GRDDS was suggested. This approach allows prolongation of the time the drug stays within the gastric environment and increases uptake and bioavailability of drug. Currently, many studies performed on GRDDS utilises systems such as expandable, floating and mucoadhesive systems. Even though recent clinical studies are shown to be promising, a lack of convincing results of necessary behaviour limits the focus on this area. Floating dosage forms appears to be one of the best approaches to use, but further studies are required in order to perfect the formulation of the system. The choice of excipient is another major effect on the systems. Thus, innovative technological advances along with suitable polymers is the key to turning research into market products.

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