Advance approaches in gastro-retentive drug delivery system and its polymers: A Comprehensive Review

Hemangi Parmeshwardas Vaishnav[1], Dr. Nishan N. Bobade[2], Aachal H. Kolhe[3], Mohini M. Murkute[4], Shritesh R. Bhoyar[5]
[1,2,3,4,5]*Vidyabharati College of Pharmacy, Camp, Amravati – 444602*

Abstract: Gastro retentive drug delivery systems have various advantages, including prolonged gastric residence time of dosage forms in the stomach for several hours, enhanced therapeutic efficiency of drugs which having narrow absorption window, and suitability for targeted release in the stomach. This review explores approaches of GRDDS, factors controlling gastric retention time, advantages, and limitation various perspectives. Present review also highlights brief collection on various polymeric material employed for Gastro retentive drug delivery systems. This provides a concise account of various attributes of recently developed approaches for GRDDS with polymeric material used.

Index term: Gastro-retentive drug delivery system, Floating delivery, Gastric retention time, polymer.

INTRODUCTION

Most of the drug delivery systems commercialized are oral drug delivery systems. This route is the most preferred route to the systemic circulation due to low treatment cost of drug, increased patient compliance, easiest way of administration and flexibility in formulation. About 90% of all drugs used are administered orally. [1]

Conventional drug delivery systems may not be able to overcome the challenges imposed by the gastrointestinal tract. just like drugs incomplete release, frequent dose requirement, and decreased dose efficiency. As a result, the inadequacy of conventional drug delivery systems to keep medications in the stomach may result in the formation of gastro retentive drug delivery system (GRDDS). These drug delivery systems have various advantages, including prolonged gastric residence time of dosage forms in the stomach for several hours, enhanced therapeutic efficiency of drugs through improved drug absorption, and suitability for targeted release in the stomach. [2] Additionally, by constantly releasing the drug for a certain period of time prior to the drug extends to absorption site, GRDDS can improve the controlled delivery of drug with an absorption window. [3]

Ideal Drug Characteristics [4]:

1. Drugs that are absorbed predominantly in the stomach e.g., Amoxicillin.
2. Drugs that degrade in the colon e.g., Metformin HCL, Ranitidine.
3. Drugs that are poorly soluble in alkaline media e.g., Furosemide, Diazepam.
4. Drugs that interrupt the normal colonic microbes e.g., Antibiotics against Helicobacter pylori
5. Drugs that are readily absorbed from the GI tract e.g., Tetracycline.
6. Drugs having a narrow absorption window e.g., Methotrexate, Levodopa.
7. Drugs that act locally in the stomach.

Basic Anatomy and Physiological Aspects of GIT:

The stomach is anatomically split into three sections: the fundus, the body, and the pylorus. The proximal stomach, which comprised of the fundus and body sections, acts as a reservoir for ingested materials, whereas the distal portion, the pylorus, is the primary site for mixing movements, functioning as a drain pump to the duodenum to achieve gastric emptying. [5]

The stomach is a part of the digestive tract that extends between the esophagus and the small intestine. The stomach contracts when it is empty, and its mucosa and submucosa are thrown up into folds called rugae. The four main kinds of secretory epithelial cells are listed below.

1. Mucous cells- secrete alkaline mucus
2. Parietal cells – secrete HCL

3. Chief cells- secrete pepsin
4. G cells- secrete hormone gastrin. [6]

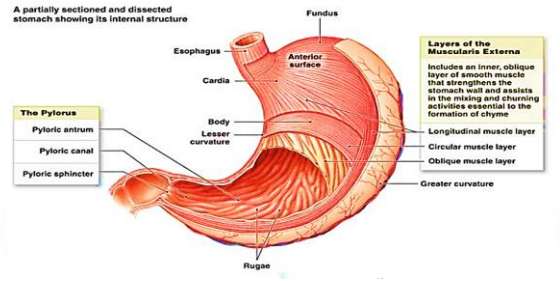

Figure 1: physiology of stomach [6]

Gastric Motility and Gastric Empty Rate –

There are two different gastrointestinal secretion and motility patterns in the fasting and fed states. The bioavailability of an orally delivered drug is dependent on the state of feeding. Fasting state is characterized by an interdigestive series of electric events known as the interdigestive migrating myoelectric cycle (MMC) or migrating motor complex. [6]. It composed of 4 phases.

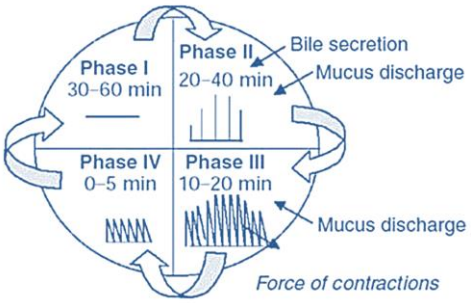

Figure 2: Phases of Gastic motility and gastric emptying rate [6]

Table I: Four phases of migrating motor complex (MMC) [7,8]

Phase	Description	Duration
Phase 1 (Basal phase)	passive state with rare contractions	last for 30-60 minutes
Phase 2 (pre-burst phase)	Intermittent contractions that grow in frequency and intensity as the phase proceeds.	last for 20-40 minutes
Phase 3 (Burst phase)	The good material relocates distally because of the regular contraction at the maximum rate.	last for 10-20 minutes
Phase 4	transitional phase between phases 3 and 1 of two successive cycles.	last for 0-5 minutes

Factor Affecting Gastric Retention of Dosage Form [9]:

- Nature of meal
- Caloric content
- Density
- Size and Shape of dosage form
- Food intake and its nature
- Effect of gender, posture and age

Advantages of GRDDS [3]:

1. For drugs with a relatively short half-life, extended release may result in a pharmacokinetic flip-flop, allowing for reduced dose frequency with enhanced patient compliance.
2. Gastroretentive drug administration can prolong and sustain the release of drug from dosage forms that involve local treatment in the small intestine and stomach.
3. The gastroretentive administration is appropriate for PH dependent absorption from the stomach, such as furosemide, captopril, diazepam, verapamil, and cefpodoxime proxetil.
4. Gastroretentive dose forms minimise drug concentration and impact variation. Then, peak concentration-related adverse impacts on concentration can be considered. It is important for narrow therapeutic index drugs.
5. This delivery system diminishes the body's counteractivity, which leads to increased drug efficiency.
6. Drug mobility is not observed, and the adequate therapeutic plasma and tissue concentrations are maintained for a long period of time. This avoids sub-therapeutics as well as toxic concentrations, lowering the risk of medical therapy failure and undesirable effects.
7. The continuous drug release from gastroretentive dosages forms delegate an extension of time beyond a critical concentration, increasing the pharmacological effects and improving the chemical effects.

Limitation of GRDDS [10]:

1. GRDDS is unsuitable for drugs that cannot withstand an acidic environment.
2. It is not suitable for drugs that are better absorbed in the inferior part of the GIT.
3. Difficulty in obtaining the desired effect and the issue of dose dumping.
4. Many factors influence stomach retention, including gastric motility, pH, and the presence of food. As a result, the dose form should be able to withstand the grinding and churning force of the stomach's peristaltic movement.
5. Inadequate in vitro and in vivo correlations.
6. The formulation is more expensive.

CLASSIFICATION OF GRDDDS:

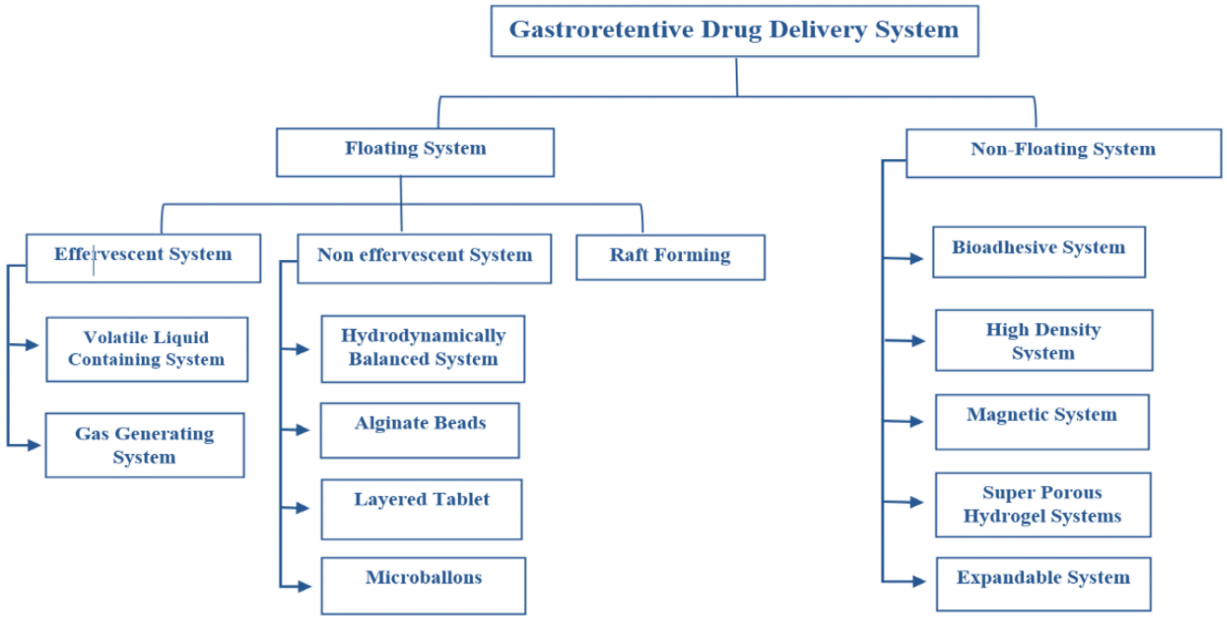

Figure 3: Flowchart showing different approaches for gastro retentive drug delivery systems

A. Floating Drug Delivery System [11]:

The bulk density of the floating drug delivery system is lower than that of gastric fluid, thus it stays in the stomach or targeted region for a longer period of time and distributes the medication in a controlled way. Over period, floating drug delivery has no effect on the rate of gastric emptying.

Characteristics of FDDS

- Release of the drug is slowed.
- serve as a drug reservoir.
- Bulk density should be less than that of gastric contents (about 1.004 - 1.0 gm/cm).
- A cohesive gel barrier must be formed.

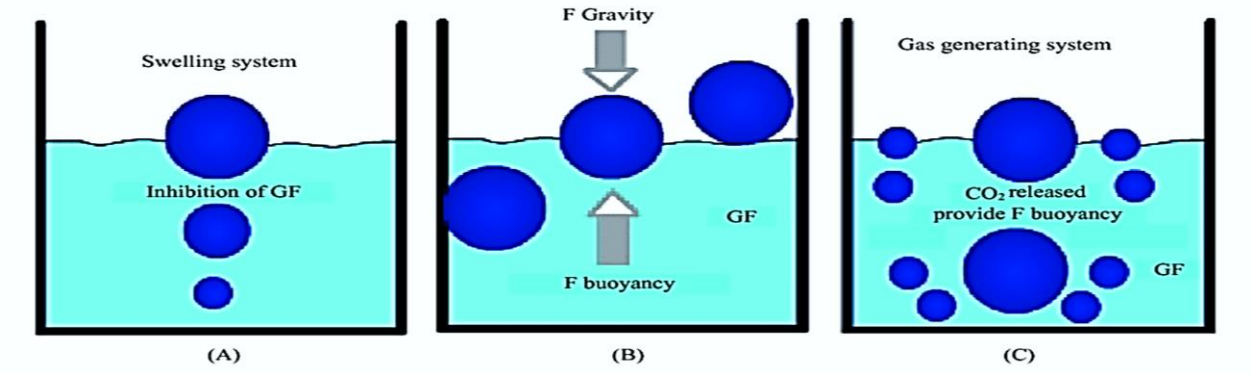

Figure 4: Mechanism of floating drug delivery system [12]:

i) Effervescent System [13]:

The effervescent system matrix is composed of swellable polymers such as tartaric acid, HPMC, and chitosan, as well as effervescent compounds such as sodium bicarbonate, citric acid, and others. Effervescent preparations may improve absorption as well as gastric pH in the GI tract. The bioavailability of effervescent tablets is higher than that of regular tablets. When sodium bicarbonate/ tartaric acid or citric acid undergoes interaction in the stomach, it produces carbon dioxide, resulting in effervescent development. The effervescent decreases the density of the tablet dosage form, allowing it to float in the stomach gastric juice. When effervescent is created in stomach fluid, the drug is kept in a reservoir and released in a controlled or sustained manner.

(a) Volatile Liquid Containing System Or Vacuum System [14]:

Recent developments in gastro-retentive drug delivery systems include vacuum or volatile liquid systems. This method consists of an inflatable chamber filled with volatile oils like ether and cyclopentane, which gasify at body temperature. The drug is releases after the release of volatile liquid. The inflatable chamber may also be filled with a bio erodible polymer plug formed of polyvinyl alcohol, polyethylene etc.

(b) Gas Generating System [15]:

The effervescent system includes the gas generating system. This device uses the effervescent reaction to liberate carbon dioxide by interacting sodium bicarbonate with citric acid. The drug enclosed in the hydrocolloid layer reduces its specific gravity and density, causing it to float over the gastric content after gas releases, gas generation, or carbon dioxide production (effervescent).

ii) Non-effervescent Systems [16]:

The drug interacts with stomach fluid in non-effervescent floating systems, causing it to swell. It maintains its form and has a density less than one, thus it floats over gastric fluid. These floating systems employ matrix-forming polymers, gel-forming hydrocolloids, or swellable hydrocolloids.

(a) Hydrodynamically Balanced Systems (HBS)

These systems are primarily composed of a drug-and-hydrocolloid mixture that creates a gelatinous barrier when it comes into contact with gastric fluid as a result of the mixture. It floats in the stomach for a prolonged period because its bulk density is less than one in gastric fluid.

(b) Alginate Beads

The interlocking agents in these systems are a hydrocolloid gel-forming agent and sodium alginate. In the presence of stomach fluid, the hydrocolloid absorbs water and creates a barrier, resulting in the trapping of air in the polymer, which causes swelling of the polymer dosage form begins to float and drug released over an extended period of time.

(c) Layered Tablets

Layered tablets are increasingly popular due to their simplicity of production, low cost, and great stability.

a. Single-Layered Floating Tablets: These tablets were produced by combining drug and gas-generating components into a matrix tablet. Because these formulations have a lower bulk density than gastric contents, they maintain buoyancy in the stomach by raising GRT. [16]:

b. Bi-Layered Floating Tablets: Bi-layer tablet has two layers: the immediate release coating, which releases the initial dose from the system, and the sustained release layer, which absorbs stomach fluid, develops impermeable colloidal gel barrier on its surface, and maintains a bulk density of less than one. [17]

(d) Microballoons

The progressive addition of a drug-containing emulsion into a volatile solvent result in microballoons. The evaporation of the solvent produces gas in a dispersed polymer. droplet, resulting in the creation of an interior aperture in the drug's polymer microsphere. It's also known as the emulsion solvent diffusion technique. [18]

iii) Raft-forming System [19]

To induce floating and prolonged medication release, a raft-forming system is composed of effervescent excipients and gel-forming polymers. These systems are room temperature tablets or liquids that can form gel when in contact with stomach juices, when the temperature increases, or when the pH changes. As a result, their behaviour can be temperature-dependent or characterised by cation-induced gelation. In either case, the development of a gel thick enough to remain

intact inside the stomach contents for hours leads to buoyancy and controlled release of drugs applications.

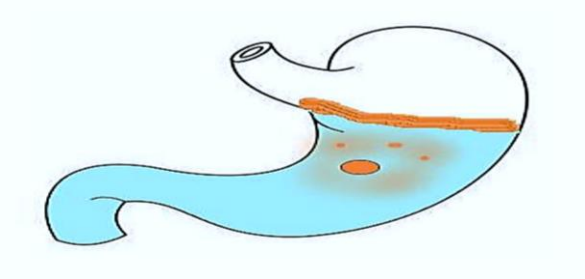

Figure 5: GRDDS based on Raft-forming system [11]

(B) Non -floating Drug Delivery System

i) Bioadhesive / Mucoadhesive Systems

This method involves incorporating drugs into a mucoadhesive agent, which may be a polymer made of natural or synthetic materials. The bond formed between the polymer and the mucosal surface promotes the mucoadhesion process [20], which is split into two stages: the contact stage and the consolidation stage [21]. In order to extend the GRT of drug compounds, it was made to adhere to the surface of gastric epithelial cells [22, 23]. Mucoadhesive polymers help to bind drug compounds to mucosal surfaces, extending drug residence duration at the site of application [24].

ii) High-Density Systems [23, 25]

The density of high-density systems is larger than that of the gastric fluid. Excipients commonly utilised in these systems include iron powder, titanium dioxide, barium sulphate, zinc oxide. The basic mechanism for attaining stomach retention is to resist peristaltic movement. Sink settle at the bottom of this non-floating system formulation to the point that it becomes immovable. The density of these formulations is larger than 3g/cm^3, which is sufficient for stand peristaltic action.

iii) Magnetic Systems [26]

This method of increasing GRT is based on the basic idea that the dosage form comprises a small internal magnet, as well as a magnet mounted on the abdomen over the site of the stomach. Although the magnetic system appears to work, the external magnet must be precisely positioned, which may affect patient compliance.

iv) Super Porous Hydrogel Systems [26]

Super porosity hydrogels with average pore size >100 µ metres swell to equilibrium size within just minute because of the rapid water absorption by capillary wetting through multiple interconnected open pores in this approach to increase gastric retention time (GRT). They swell to a considerable size (swelling ratio: 100 or above) and are designed to be mechanically strong enough to withstand pressure from stomach contraction.

v) Expandable System [27]

GRDDS is also defined as folded systems. The dose form expands in the stomach via swelling or unfolding. Mechanical form retention causes the unfolding. Swelling is mainly caused by diffusion.

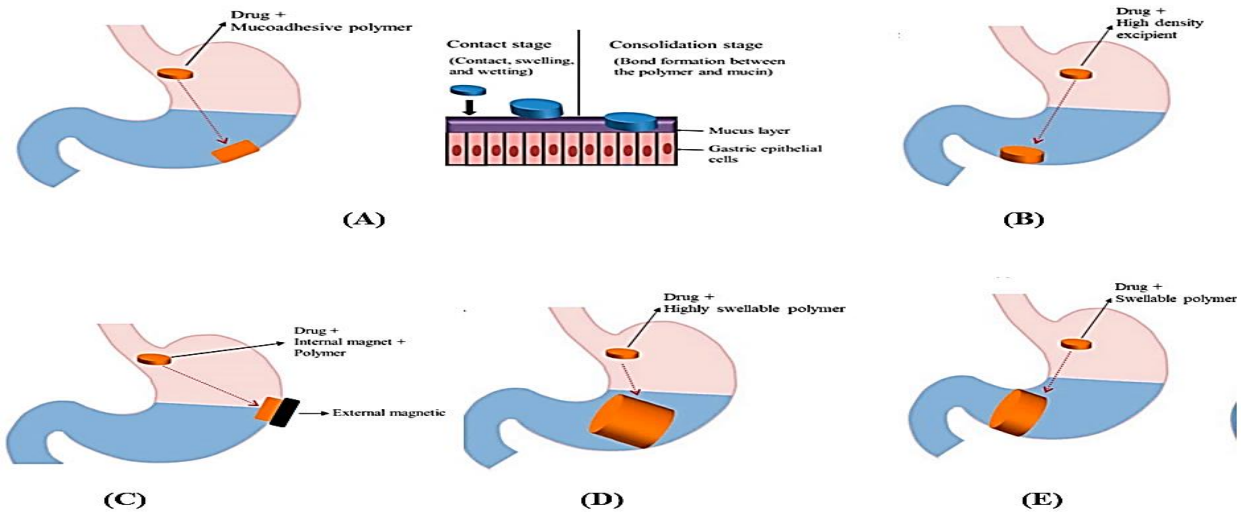

Figure 6: (A) - Bioadhesive/Mucoadhesive Systems; (B) - High-Density Systems;
(C) - Magnetic Systems; (D) - Super porous hydrogel systems; (E) - Expandable system (2)

POLYMERIC MATERIALS IN GASTRORETENTIVE FORMULATIONS

Based on their origin, the several polymers employed in GRDDS may be divided into two categories.

A) Synthetic Polymers

i. Hydroxy Propyl Methyl Cellulose (HPMC)

The most common hydrophilic carrier material utilised in the formulation of oral controlled controlled delivery systems is hydroxypropyl methylcellulose [28]. HPMC, also known as hypromellose, is a cellulose ether in which one or more of the three hydroxyl groups from cellulose glucopyranose units have been replaced, resulting in ether linkages. Thus, it is a semisynthetic polymer derived from highly purified natural pulp and etherified with a mixture of methyl chloride and propylene oxide to generate a water-soluble, non-ionic cellulose ether [29]. Methocel® and Pharmacoat® are the brand names for the most widely used marketed HPMC.

ii. Hydroxypropyl Cellulose (HPC) and Hydroxyethyl Cellulose (HEC)

HPC has been used as the principal matrixforming polymer in formulations made utilising hot-melt extrusion and 3D printing methods because of its low Tg, indicating that the formulations may be treated at a low temperature. HPC has demonstrated its capacity to create bioadhesive films [30]. The effect of several additives on the bioadhesive properties of HPC-based films was investigated, that including Carbomer 971P and a polycarbophil into HPC films significantly improved bioadhesion when compared to film containing HPC and PEG 3350.

Hydroxyethyl cellulose (HEC) is used as a gelling and thickening ingredient in the construction of biostructures for the delivery of hydrophobic pharmaceuticals [31]. Hydroxyethyl cellulose (HEC), like HPC, has been added in multicomponent polymeric matrices to give the requisite gastro-retentive characteristics.

iii. Carboxy Methyl Cellulose (CMC)

The cellulose derivative CMC, which has carboxymethyl groups (-CH2-COOH) connected by an ether bond to some of the hydroxyl groups of the glucopyranose monomer units of the cellulose backbone, is semi-synthetic, non-toxic, and water-soluble. Because the carboxylate groups in sodium CMC are anionic, interactions with non-ionic hydrocolloids such as HPMC and HEC may improve their gel-viscosity properties [31].

iv. Eudragit (Polymeric Methacrylate) [32]

Eudragits are available in the form of dry powders and emulsions. To dissolve Eudragit, a 60:40 mixture of acetone and isopropanol is used. Eudragit S 100, which exists as a powder and is used for enteric coating, is dissolved in 95% acetone and alcohol to allow pH 7 release in enteric fluid. They may dissolve promptly in neutral to weak basic solutions and produce membrane sheaths that are resistant to stomach juice but erodible in intestinal fluid. Eudragits are mostly used as a coating in oral capsules and tablets. Film melting varies depending on the type of polymer utilised. Acetone and ethyl alcohol both assist to dissolve Eudragit S 100. Because of their resistance to stomach fluid, Eudragit species are used in enteric coating. Water insoluble film coating might be created in extended-release dosage forms using Eudragit RL, RS, NE 30D, NE 40D, and NM30D. Eudragit RL generates more permeable films than Eudragit RS and combining them allows for varied permeability. To regulate the dissolving of the tablets, larger volumes (5e20%) of dry Eudragit are used. Dried polymers are used in direct compression in percentages ranging from 10% to 50%.

v. Ethyl Cellulose [32]

Ethocel (Ethylcellulose) is used in pharmaceutical for a variety of reasons, including disguising the bitter taste of some medications, moisture protection, stabilising, extended-release multi-particle coating, precision packing, and prolonged release. Ethocel is insoluble in water. And it does not dissolve in stomach acidity; nevertheless, it swells in the stomach and becomes permeable to water, allowing for prolonged release. Several types of Ethocel have been approved for usage in extended-release solid dosage and GRDDS. There are various varieties of ethylcellulose, each with its own viscosity and chain length.

vi. Crosslinked Polyacrylates: Carbomers, Carbopol® and Polycarbophyl (PCP) [33]

Carbomers are high-molecular-weight polyacrylic acids that have been crosslinked with polyalcohol allyl ethers such as pentaerythritol polyallylether and polyallyl sucrose. Carbomers are weak acids with a reported pKa of 6.0 (0.5). Carbopol® polymer is a Carbomers product brand name (Lubrizol Corporation). Polycarbophil is the USP/NF

compendial term for another family of polyacrylic acids that are weakly cross-linked with divinyl glycol (and calcium ions) and are registered as Noveon® polymers. At neutral pH, polycarbophil may absorb roughly 100 times its weight in water.

vii. Crospovidone: Crosslinked Poly (N-vinyl pyrrolidone) (PVPP) [33]

Crospovidone (Polyplasdone®, Kollidon CL) is a synthetic cross-linked PVP that is insoluble in water. Crospovidone swell without gelling, which is useful for making orally disintegrating tablets (concentration of 2-5% w/w). The intra-particular porosity rises with particle size, resulting in more water absorption and quicker disintegration. Because crospovidone is nonionic, its disintegration efficiency is independent of medium pH, making it a potentially appropriate disintegrant for cationic drugs. This polymer can also be utilised to improve the solubility of poorly soluble drugs during the coevaporation process. This method allows the drug to adsorb onto crospovidone in the presence of an appropriate solvent, and when the solvent is evaporated, a solid combination with a quicker drug dissolution rate is produced. Crospovidone is sometimes used in highly hydrophilic matrices, such as combinations with polyacrylic acid and xanthan gum. These polymers were discovered to have outstanding swellable characteristics at a weight ratio of 1:1:1.

viii. Sodium Croscarmellose. Cross-linked Sodium Carboxymethyl Cellulose [33]

Sodium croscarmellose (Ac-Di-Sol®) is an internally cross-linked sodium carboxymethylcellulose utilised as a superdisintegrant in pharmaceutical formulations. This substance is an insoluble and hydrophilic polymer with improved long-term stability. The cross-linking limits water solubility while yet allowing the material to expand and absorb several times its weight in water. As a result, it enhanced drug solubility and disintegration qualities, enhancing formulations subsequent bioavailability by putting active components into closer interaction with body fluids. It is employed in the co-formulation of hydrophilic particulate materials. This polymer performs exceptionally well in direct compression, dry granulation, and wet granulation processes.

ix. Poly (vinyl acetate) (PVA) [33]

PVA is a thermoplastic hydrophobic polymer that is soluble in organic solvents. It is brittle below its Tg (about 305K) and very sticky above it. This plastic material's emulsions, which are manufactured on a large scale, are economical and have high adherence to numerous porous surfaces. PVAc is utilised as a coating polymer and as a film-forming component in water-based formulations. It can offer flexible and water permeable coatings to tablets or other oral formulations. It is also utilised as an adhesive, plasticizer, and thickener in a variety of applications.

x. Gelucire® [33]

Gelucire® is a class of poly(ethylene glycol)-based (PEG) surfactants generated from mono, di, and triglyceride mix with PEG esters of fatty acids that are frequently utilised in pharmaceutical formulations. By varying the molecular weights of PEG and fatty acid, Gelucire-based surfactants with a wide range of HLB and melting point values (33-65 C) are produced. As a result, Gelucire® grades are called after their melting point (the first figure) and the HLB (the second value). Gelucire 39/01, for example, has an HLB value of 1 and a melting point of 39 C. Gelucire is divided into hydrophilic and hydrophobic grades based on its HLB values. Gelucire with HLB values less than 6 are hydrophobic; HLB values 6-9 are water dispersible; and HLB values greater than 9 are hydrophilic. Hydrophilic grades include Gelucire 50/13, 44/14, 48/16, 55/18, 35/10, and 48/09, whereas hydrophobic grades include Gelucire 43/01, 39/01, 33/01, 50/02, 54/02, and 64/02. The hydrophobic G43/01 and G39/01 grades, as well as the hydrophilic G50/13 and G44/14 grades, are the most commonly employed in GRDDS and are found in multi-unit floating systems. Without the presence of gas producing agents, sustained-release floating minitablets were prepared using G43/01 and G39/01. They are commonly employed to improve drug solubility and wettability.

xi. Polycarbophil [34]

It is a controlled release tablet binder that also is adsorbent and bioadhesive. The utilisation of floating-bioadhesive microspheres coated with poly carbophil as a gastro retentive drug delivery method for the treatment of Helicobacter pylori has been discovered.

xii. Alginic Acid [34]

It functions as a stabilising agent, a suspending agent, a sustained release adjuvant, and a tablet binder. The release capabilities of alginate gel beads capable of floating in the stomach cavity have been found to be

suitable for prolonged release of drugs and targeting the gastric mucosa.

B) Natural Polymers

They are derived from plants. They are also hydrophilic carbohydrate polymers. They are insoluble in organic solvent and were discussed:

i. Chitosan [35]

Chitosan is a chitin N-deacetylated derivative. Chitosan, which includes the main amino group, exhibits regulated release action, mucoadhesive characteristics, in-situ gelation, and increased permeability. Chitosan is a non-toxic, biodegradable, and biocompatible polymer that may be used for oral extended-release tablets by granulation or simply direct compression.

ii. Guar Gum [35]

It is derived naturally from Cyamopsis tetragonolobus species and is non-ionic in nature. Guar gum is a polysaccharide with a molecular weight ranging from 50,000 to 8,000,000. When dissolved in water, they exhibit gelling qualities as well as prolonged release action.

iii. Xanthan Gum [35]

It is derived from aerobic fermented carbohydrates from Xanthomonas compestris species and includes glucose, glucuronic acid, and mannose. It is not employed or exhibits prolonged drug release in zero-order kinetics for formulation to sustained drug release.

iv. Pectin [35]

Pectin is a biopolymer that has the ability to produce gels. It is derived from the plant's cell wall. It has a bioadhesive nature. Pectin not only exhibits sustained releasing activity, but it also functions as a drug carrier in targeted treatment.

v. Gellan Gum [36]

Gellan gum can be used for in-situ gel formation, when Ca2+ ions are available as a crosslinking agent. It can be used as a crosslinking agent in in-situ gels when combined with Ca2+ ions.

vi. Carrageenans [36]

Carrageenans are high-molecular-weight anionic polysaccharides. Because of their high durability, excellent compatibility, and persistent viscoelasticity of the tablet throughout granulation and compression, they proved useful as tablet excipient agents. Carrageenans are thus suitable excipients for long-acting formulations. Significantly, the carrageenans actual density measurements were found to be substantially higher than those of the cellulose ethers (MC, HPMC, NaCMC and HPC).

Table II: Polymers in different dosage form

Sr.no	Dosage form	Polymer
1.	Tablets	Hydroxypropyl Methylcellulose (HPMC K4M, HPMC K100M) HPMC E15LV, HPMC E50LV, HPMC K100LV, HPMC K15M, Sodium Carboxymethyl Cellulose, Crospovidone, Xanthan Gum, Karaya Gum, Guar Gum, Carrageenan.
2.	Microspheres	Polymethacrylate, Polyacrylamine, Ethylcellulose, Eudragit RL100, Cellulose Acetate, Polycarbophil
3.	Matrix tablet	HPMC K4M, HPMC K15M, HPMC K100K, Ethyl Cellulose.
4.	Floating beads	Sodium Alginate, Calcium Alginate, HPMC K4m, Hydroxy Ethyl Cellulose, Alginic Acid, Guar Gum, Sterculia Gum, Gelatin, Pectin
5.	Superporous hydrogel	HPMC, Carbopol 934P, Ethyl Cellulose, Chitosan, Sodium Carboxymethyl Cellulose, Gellan Gum
6.	Microballoons	polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar, pectin etc.
7.	Floating pellets	methocel K4M, methocel K100LV, sodium alginate, Gelucire

CONCLUSION

GRDDS are an important approach for extending drug retention, performing controlled release, and improving their absorption and bioavailability. Gastroretentive drug delivery systems, providing optimum benefit to patients while ensuring maximum patient compliance. Polymeric compound has a crucial service in retaining numerous active substances in dosage form in the stomach, either by floating or via any other mechanisms. Polymeric material used in gastro retentive drug delivery systems type and their role was described in depth.

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