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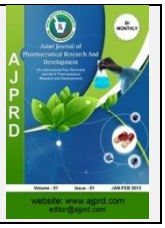

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Review Article

A Review for Gastro - Retentive Drug Delivery System

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A B S T R A C T

Inadequate pharmacokinetic properties may be connected with the widespread use of oral dose forms in disease treatment. Because of the formulation's rapid transit through the gastrointestinal tract (GIT), it can be challenging to achieve therapeutic levels of the medicine in specific situations when it is barely soluble; In addition, some medications must work locally due to a gastric disease, although they only last a short period in the stomach. Numerous studies have been done to identify formulations that can enhance all of these characteristics while extending stomach residence time. Many orally delivered medications advantageous for from the extended stomach retention time provided by gastroretentive controlled drug delivery systems.With a focus on current methods for extending stomach residence duration, the study's objective was to examine, gather, and present the preceding and contemporary literatures in a shorter format. The current review briefly discusses the need for GRDDS., Pharmaceutical importance's of GRDDS, Physiology of stomach, Stomach functionalities, Approaches of GRDDS, factors controlling gastric retention, advantages , disadvantages, Method of preparation of Gastro-retentive Multiparticulate system, Polymeric material in gastroretentive formulations, Evaluation of Gastroretentive dosage form, comparsion between Conventional and Gastroretentive drug delivery system.

Key Words: Gastroretentive Controlled Drug Delivery Systems, GRDDS, Gastric Retention

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INTRODUCTION

Oral drug administration has traditionally been the main method of drug delivery. Over the past two decades , a variety of oral delivery systems have been developed to operate as drug reservoirs from which the active ingredient can be given over a predefined amount of time at a controlled rate.

However, there are various physiological issues with this technique. Including a variable and unpredictable stomach emptying rate, the availability of a drug absorption window in the upper small intestine for a variety of drugs, and a brief gastrointestinal transit time (8–12 hours)[1].To address these issues, Researchers have created a drug delivery method that lasts an extended period of time in the stomach and predictable period of time. An effort is being made to create a drug delivery system that can deliver a therapeutically effective plasma drug concentration for a longer period of time, reducing the frequency of dosing and minimising fluctuation in plasma drug concentration at steady state[2].

GRDDS is characterised as a system that remains in the stomach for a sufficient duration of time before releasing active moiety in a regulated manner and being metabolised throughout the body. Numerous GRDDS that extend GRT have been developed over the past 20 years. The main goal of developing GRDDS is to reduce the issues with the current oral sustained release dose form and to create patient-beneficial medication delivery[3].

One novel method in this field is the GRDDS (gastro retentive drug delivery system). GRDDs are dose forms that the stomach is able to maintain. GRDDSs can improve the regulated administration of drugs with an absorption window by continuously releasing the drug for a long time before it reaches its absorption site[4]. For medications that are absorbed from the proximal section of the GIT (gastro intestinal tract), are less soluble in alkaline pH, are destroyed by alkaline pH, or come into contact at the lower part of the GIT, prolonging the stomach retention of the drugs may occasionally be beneficial to provide therapeutic

benefits. GRDDS are advantageous for such medications by enhancing theirBioavailability ,Therapeutics efficiency,Possible dosage reduction, Apart from these benefits, these systems provide other pharmacokinetic benefits such as the maintenance of consistent therapeutic levels above a long period of time and hence a reduction in therapeutic level[5].

Short-half-life drugs and easy absorption from the GIT are quickly removed from the systemic circulation. To ensure appropriate therapeutic activity, these medicines must be dosed often. The development of oral sustained controlled release formulations attempts to overcome this limitation by gradually releasing the medication into the GIT while preserving drugs concentration that is efficient in the systemic circulation for a longer duration of time. Using such drug delivery would stay in the stomach after oral administration and release the medication in a controlled way, allowing the drug to be continuously supplied to its absorption sites in the GIT[6].

GRDD devices help with drug absorption over the predetermined period of time by staying for a longer period of time in the stomach than conventional site-specific drug delivery systems. The following improve as a result: the bioavailability, decrease drug waste, enhances the solubility of medications which are less soluble in environments with high pH levels (such as weakly basic medications like domperidone and papaverine), it also helps in obtaining drug deliveryloacally to the stomach and proximal small intestine.

When creating a site-specific orally given controlled release dosage form, it is desirable to establish longer gastro residence duration via drug delivery.

Additionally, prolonged gastric retention of the therapeutic moiety can offer a number of advantages for the local and prolonged delivery of drugs to the stomach and proximal small intestine to treat certain disorders, including[5]-: Improved bioavailability ,Improved therapeutic efficacy ,Possible dose reduction, Improves the drug solubility, which is less soluble in high pH environment for example, weakly basic medications like Domperidone, papaverine, etc., Reduce drug waste, help in attaining local drug distribution to the stomach and proximal small intestine.

For local action in the upper section of the small intestine, such as the treatment of peptic ulcers, prolonged gastric retention time in the stomach may be advantageous[7].

Oral dose formulations for stomach retention have received increasing interest in recent years due to their therapeutic benefit in allowing control over the timing and site of medication release. Many medications classified as once-a-day delivery have demonstrated on dosage form transit time. As a result, a system intended for extended stomach retention will extend the time available for drug absorption in the small intestine[8].

The mechanism of solid dose forms' regulated gastric retention may include Flotation, Sedimentation, Expansion, Modified shape systems or by the simultaneous administration of pharmacological agents that delay gastric emptying

Why the need of GRDDS?

Certain medications that have been absorbed through the gastrointestinal tract (typically with short half-lives) are quickly eliminated from the circulatory system, necessitating regular dosing. Innovative technique Gastro-retentive medication deliveries devices are used to address this issue.They have high plasma drug concentration, which reduces dose frequency. Another advantage of this approach is that it eliminates variability in plasma drug concentration by delivering the drug in a regulated and consistent manner [9]. The rationale for the use of GRDDS is shown in Figure No1.[10]

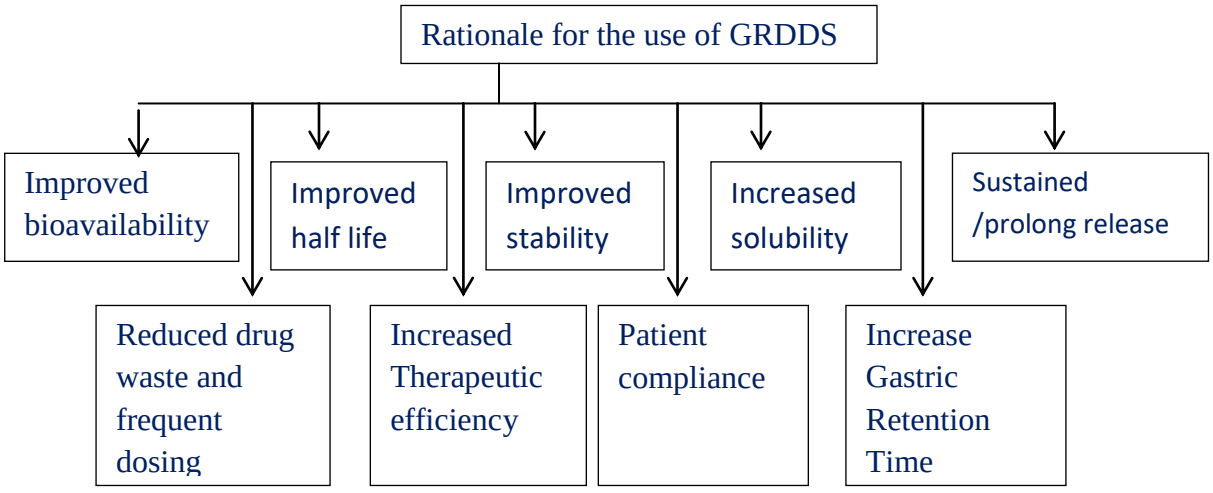

Figure No 1: Rationale for the use of GRDDS

Importance of GRDDS in the field of Pharmaceutics

Immediate release oral delivery methods are the most commonly employed to treat disease because they are absorbed only at a specific place. The disadvantages of the instant release dosage form necessitate the development of Gastro-retentive drug delivery methods. These systems will aid in the retention of drugs at specific sites for extended periods of time. This is accomplished by keeping the dosage form in the stomach and releasing the drug in controlled action at particular locations in the stomach, duodenum, and intestine [11].

Physiology of the Stomach

GRDDS success is dependent on an understanding of stomach physiology and the accompanying gastric emptying process. As shown in Figure No. 2, the human stomach is divided into three anatomical regions: the fundus, the body, and the antrum (pylorus). The typical volume of a stomach after a meal is roughly 1.5 l, which varies between 250 and 500 ml during the inter-digestive stages [12]. The section composed of the fundus and the body serves as a reservoir for any undigested material, whereas the antrum is the primary site for mixing action. The antrum, being the lower section, acts as a pump for gastric emptying through a pushing action.Pylorus separates the stomach from the duodenum and influences the gastric residence period of ingested items. However, the pattern of stomach motility differs between fasting and fed states [13]. The stomach motility pattern is organised into active and dormant cycles.Each cycle lasts 90-120 minutes and includes four phases, as shown in Table No.1 [14]. The stomach motility pattern is known as migrating motor complex (MMC) [15].

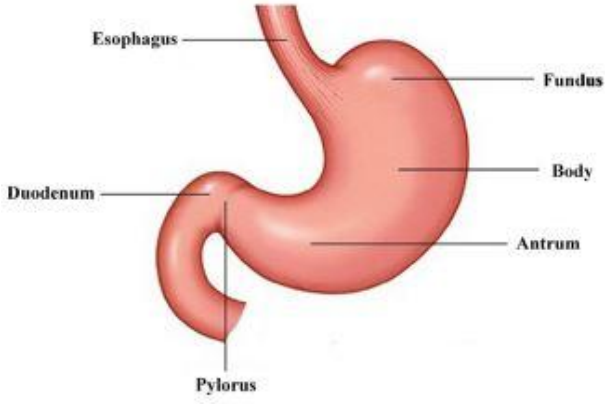

Figure No 2: Human Stomach

Table No 1: Four phases of migrating motor complex (MMC) [14]

Phase	Description	Duration[min]
Phase 1 [basal phase]	Idle state without any contraction	30 to 60
Phase 2 [pre-burst phase]	Intermittent contraction	20 to 40
Phase 3 [burst phase]	The regular contraction at the maximal frequency causes the good material to migrate distally.	10 to 20
Phase 4	Transition period between phase 3 and phase 1	0 to 5

Stomach Functionalities

- The stomach performs the following functions[16]
- Temporary storage to allow digestive enzymes, pepsins to act
- Pepsins are enzymes that break proteins down into polypeptides.
- Mechanical breakdown- the three smooth muscle layers let the stomach to serve as a churn, adding gastric juice and liquifying the contents to chime. Parasympathetic nerve stimulation has enhanced gastric motility and output.
- Water, alcohol, and several lipid-soluble medications are examples of substances that limit absorption.
- Non-specific microbial defence supplied by hydrolytic acid in gastric juice. Vomiting can occur as a result of ingesting stomach irritants such as bacteria or chemicals.
- Iron preparation for absorption- the acid environment of the stomach dissolves iron salts, which are required for iron absorption in the small intestine.
- Production and secretion of intrinsic factor needed for absorption of vitamin B12 in the terminal ileum.
- Regulation of the passage of gastric contents into the duodenum. The pylorus pushes tiny jets of stomach contents through the pyloric sphincter in the duodenum when the chyme is sufficiently acidified and liquefied. The sphincter is normally closed, preventing, backflow of chime into the stomach.

Approaches for achieving gastric retention

There are several techniques to developing gastro retentive medication delivery devices. Figure 3 depicts some of the ways.

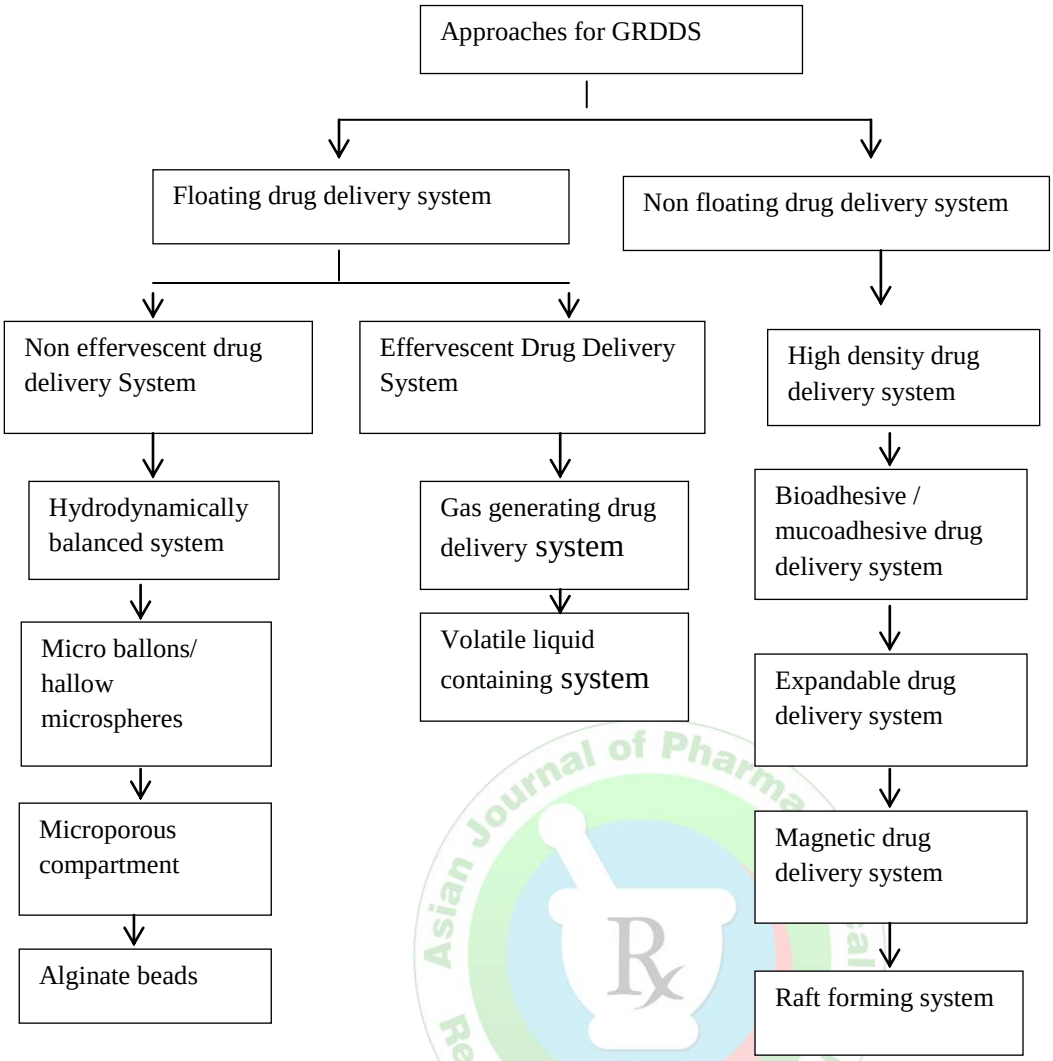

Figure No 3: Approaches of GRDDS

Non-floating drug delivery systems

1. High density (sinking) drug delivery system

The formulation's density exceeds the density of normal stomach content. The materials boost density to 1.5-2.4 gm/cm³. The GI transit time of pellets can be extended from 5.8 to 24 hours depending on density. However, the efficiency of this method in humans has not been demonstrated, and no formulation has been commercialized [17].

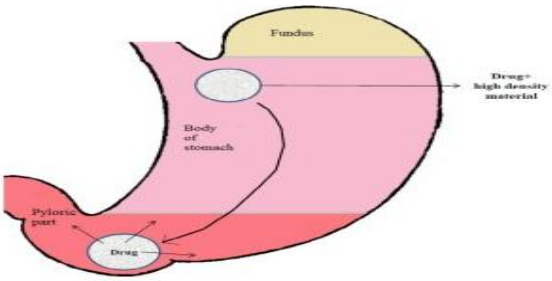

Figure No 4: High density drug delivery system

2. Bioadhesive or mucoadhesive drug delivery system

The gastric retention time has extended by adhering the bioadhesive system for gastric mucous membrane.The delivery system's adhesion to the stomach wall prolongs residence time, enhancing bioavailability. Chemicals used for mucoadhesion include gliadin, carbopol, lecithin, chitosan, polycarbophil, and carboxymethyl cellulose [18].Novel adhesive materials produced from bacteria fimbrae or synthetic counterparts have also been tested for adhesion to the gut. However, the gastric mucoadhesive force is insufficient to resist the propulsion force of the stomach wall. Another disadvantage of this sort of system is the continual production of mucus and dilution of the gastric content. Many researchers have experimented with a synergistic method involving floating and a bioadhesion system (Figure No. 5: Mucoadhesive drug delivery system).

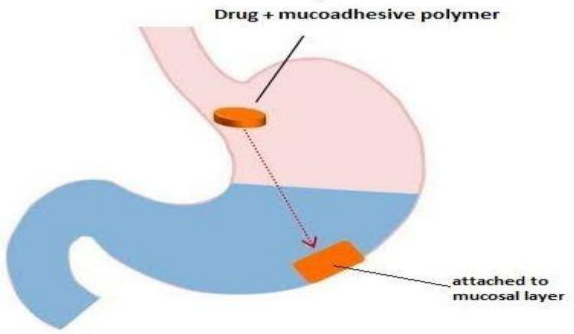

Figure No 5: Bioadhesive or mucoadhesive drug delivery system

3. Magnetic system

The dose form incorporates a small magnet in this method, and another magnet is placed on the abdomen above the position of the stomach. The external magnet should be set with precision, which may reduce patient compliance.

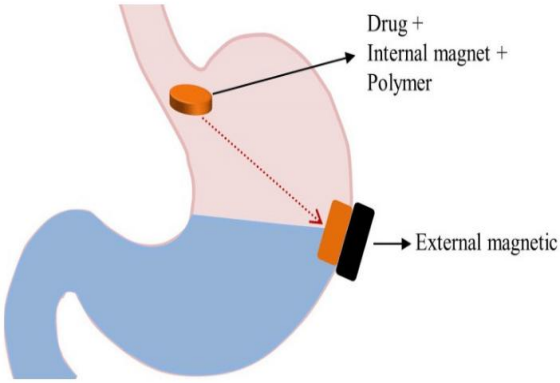

Figure No 6: Magnetic system

4. Expandable System

These systems have the ability to enlarge and stay in the stomach for prolonged periods of time. These are frequently presented in the form of capsules that include a folded and compressed dosing form. The dosage form expands and the capsule shell breaks down in the stomach environment, making it unable to pass through. Drug distribution that is maintained and under control can be accomplished by employing the right polymer.

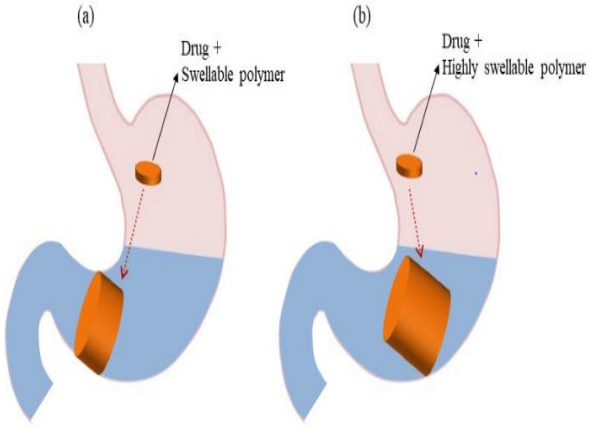

Figure No 7: Expandable System

5. Raft forming systems

To achieve sustained drug delivery, these systems are built with gel-forming polymers and effervescent excipients. Because they provide a barrier between the oesophagus and the stomach, these systems are good at achieving a localised impact. As a result, the device can be used to treat peptic ulcers and gastroesophageal reflux disease. When these systems come into touch with stomach fluid, they swell and create a viscous cohesive gel, resulting in the formation of a continuous layer known as a raft[19,20]. The antacid raft forming method, which uses sodium alginate as a gel forming polymer, sodium bicarbonate, and acid neutralizer as gas generating agents, was also recently created. The raft floats on the gastric fluid due to CO2 production, which reduces the system's bulk density. The raft can float on the gastric fluid for several hours and release the medicine continuously. These rafts are particularly useful for delivering antacid medications [21]. Because of their low mechanical strength, these systems are exposed to MMC[20,22].

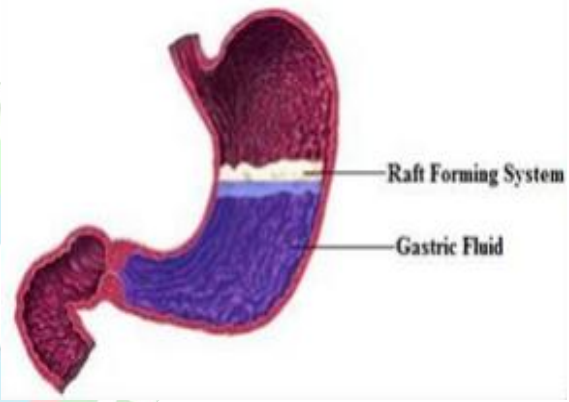

Figure No 8: Raft forming systems

Floating Drug Delivery System

Mechanism of floating drug delivery system

Floating drug delivery systems (FDDS) float in the stomach for a long time without slowing down the gastric emptying rate since they have a lower bulk density than gastric fluids. As depicted in Figure No. 9(a), the medication is gradually released from the body at the required pace while the system is floating on the contents of the stomach. To maintain the dose form consistently buoyant on the surface of the meal, however, a minimal amount of floating force (F) is also necessary in addition to the minimal stomach content needed to achieve the buoyancy retention principle. The literature has established a specific method for calculating resultant weight to evaluate the dynamics of the floating force. The equipment works by continually measuring the force equivalent to F (as a function of time) required to keep the submerged object submerged. If F is on the positive side, the object floats better, as seen in Figure No. 9. This equipment helps to optimise FDDS in terms of the stability and lifespan of the created floating forces, avoiding the negative effects of unanticipated intragastric buoyancy capacity changes[23].

F = F buoyancy – F gravity = (Df – Ds) gv

Where, F= total vertical force, Df = fluid density,Ds= object density, v = volume, g = acceleration due to gravity

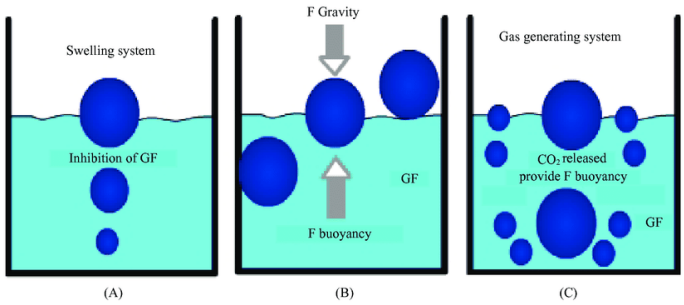

Figure No 9: Mechanism of floating drug delivery system

1. Effervescent System

These systems was further classified into

a. Gas generating System

The main process at work in this system is the formation of CO2 gas as a result of the reaction of sodium bicarbonate, citric acid, and tartaric acid. The gas created reduces the density of the system, causing it to float on the stomach juices. Salts and citric/tartaric acid emit CO2, which becomes trapped in the system's jellified hydrocolloid layer, lowering its specific gravity and causing it to float over the chime[24]. The system is made up of a sustain release pill as the seed, which is surrounded by a double layer. The inner layer is a bubbly layer comprising sodium bicarbonate and tartaric acid. The outer layer is a PVA shellac-containing swellable membrane layer. (Figure No.10: effervescent drug delivery method.)

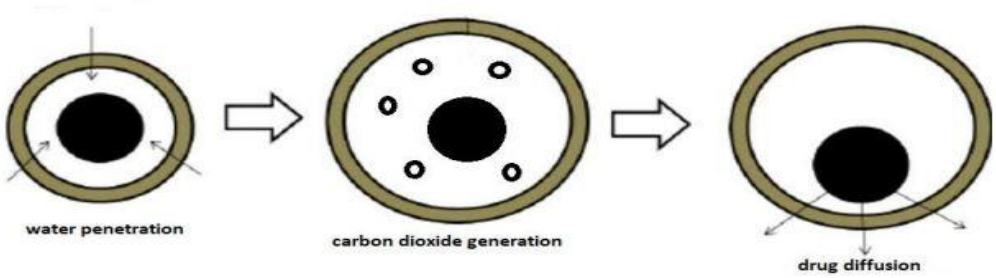

Figure No 10: Gas generating System

b. Volatile liquid containing system

These have an inflatable chamber that holds a liquid, such as ether or cyclopentane, which gasifies at body temperature and causes the chamber in the stomach to inflate. These systems osmotically regulate a floating system with a specified hollow unit. The system has two chambers, the first containing the medicine and the second containing the volatile system. These systems are further classified as follows:

- **Intra gastric floating gastrointestinal drug delivery system-**

This method includes a flotation chamber filled with vacuum or an inert, harmless gas, as well as a micro porosity compartment containing a medication reservoir.

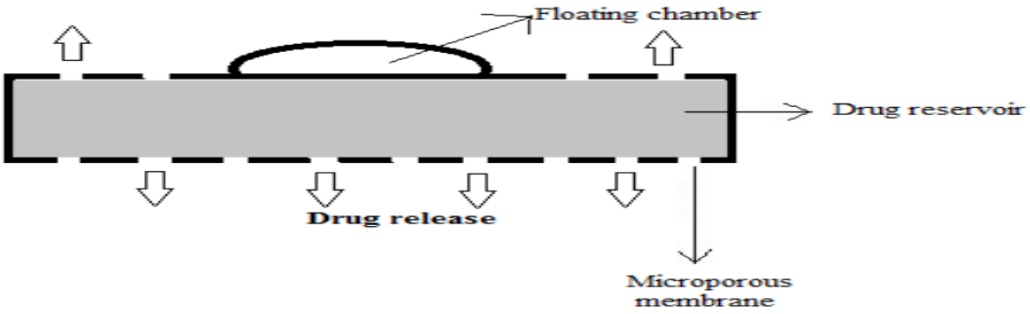

Figure No 11: Intra gastric floating gastrointestinal drug delivery system

- **Inflatable gastrointestinal drug delivery system-**

At body temperature, an inflatable chamber holding liquid ether gasifiers to inflate the stomach. The inflatable chamber contains bioerodible polymer filament (e.g., a copolymer of polyvinyl alcohol and polyethylene) that gradually dissolves in gastric fluid, causing the inflated chamber to release gas and collapse.

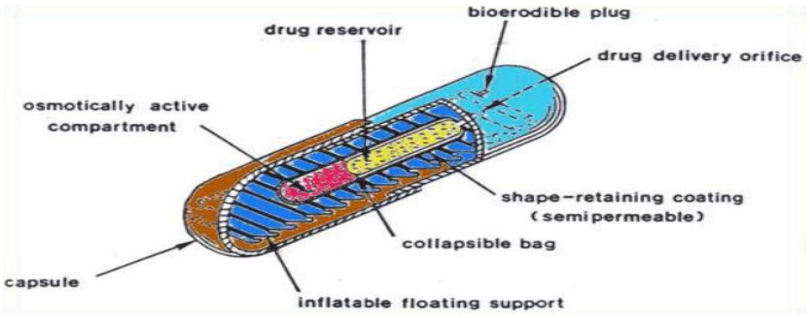

Figure No 12: Inflatable gastrointestinal drug delivery system

- **Intra-gastric osmotically controlled drug delivery system-**

It is made up of an inflatable floating capsule and an osmotic pressure regulated medication delivery system.The inflatable capsule disintegrates in the stomach, releasing the osmotically regulated drug delivery system, which is made up of two parts: a drug reservoir compartment and an osmotically active compartment. Working on this method, superporous hydrogels are a good example. The dose form expands to several times its original volume when it comes in contact with gastric fluid. Due to the dose form's bigger size, the gastric contraction slips over the system's surface, pushing the dosage form back into the stomach after the gastric contraction has pushed it to the pylorus.

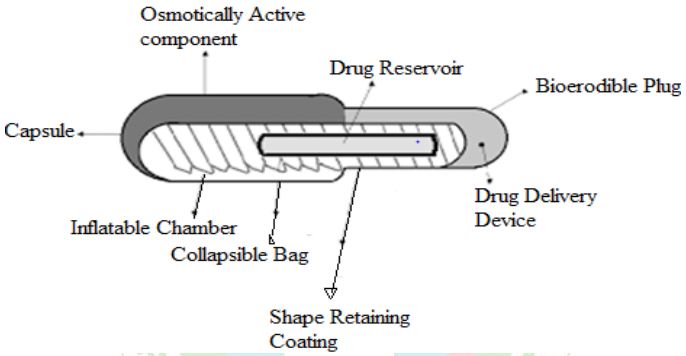

Figure No 13: Intra-gastric osmotically controlled drug delivery system

2. Non-effervescent system [25]

a. Hydrodynamically balanced system

It is a medication formulation containing gel-forming hydrocolloids designed to remain buoyant in the stomach contents.Because drug delivery systems have a lower bulk density than gastric fluids, they can float in the stomach for an extended period of time without altering the gastric emptying rate. The medicine is gently released from the system while the system is floating on the gastric contents at the desired rate. Following the system's slow release at the desired rate. The residual system is emptied from the stomach once the medication is released. As a result, GRT increases and variations in plasma medication concentrations are better controlled.

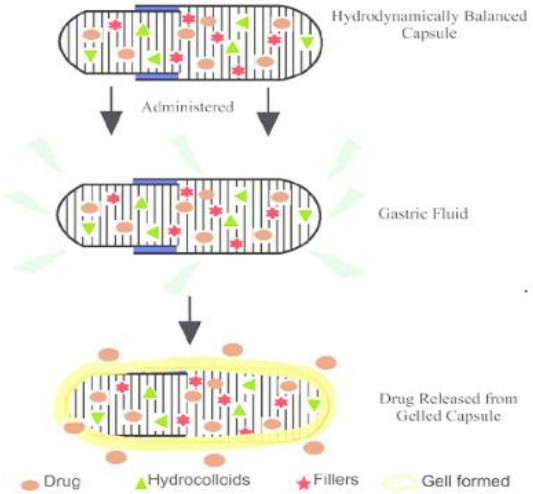

Figure No 14: Hydrodynamically balanced system

b. Micro balloons

Micro balloons (Hollow microspheres) are, strictly speaking, empty spherical particles with no core. These microspheres are often free-flowing powders made of proteins or synthetic polymers, with a size of fewer than 200 micrometres. To construct a hollow inner core in micro balloons loaded with medicine in their outer polymer shell, innovative technologies such as solvent evaporation are used. The medication and an enteric acrylic polymer mixture are dissolved in an ethanol/dichloromethane solution, which is then put into an agitated solution of Poly Vinyl Alcohol (PVA) that is thermally regulated at 40°C .After the emulsion has solidified into a stable state, the organic solvent is removed from the mixture by raising the temperature under pressure or by constant stirring. Dichloromethane evaporates in the droplet of dispersed polymer to form the gas phase inside the hollow interior cavity of the polymer microsphere.

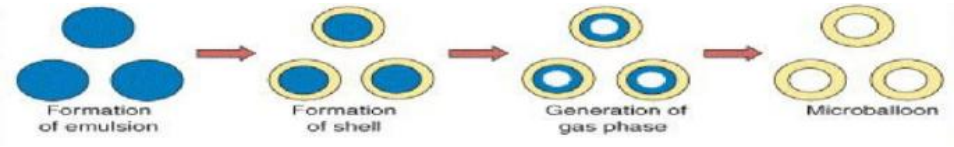

Figure No 15: Micro balloons

c. Microporous compartment

The drug reservoir is contained inside a microporous compartment with pores along its top and bottom walls in this arrangement. The delivery system floats over the gastric fluid, which enters through the aperture, dissolves the medicine, and transports the dissolved drug to the stomach and proximal part of the small intestine for absorption.

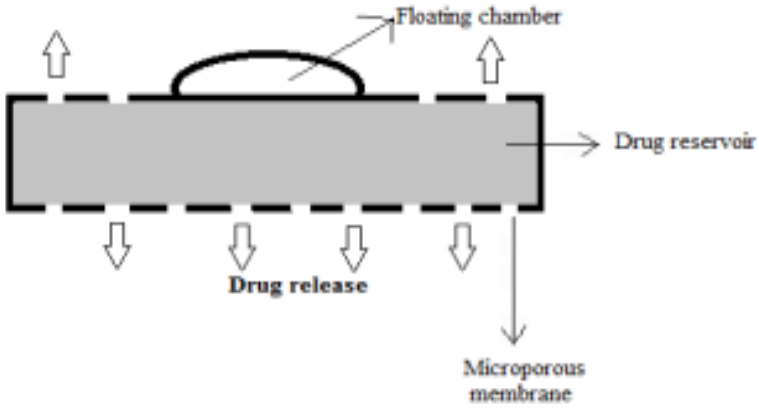

Figure No 16: Microporous compartment

d. Alginate beads

Calcium alginates that have been freeze dried have been used to create multi unit floating dosage forms [26]. Spherical beads of about 2.5 mm diameter can be made by dropping sodium alginate solution into an aqueous solution containing calcium chloride. These beads are separated and dried by air. As a result, an aporous system forms, which remains buoyant in the stomach.

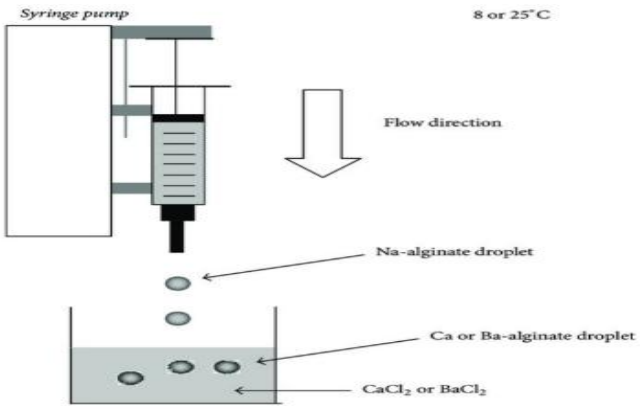

Figure No 17: Alginate beads

Factors controlling GRDDS [27,28,29]

Factors controlling GRDDS are shown in Figure 18 and some of the factors are enumerated below

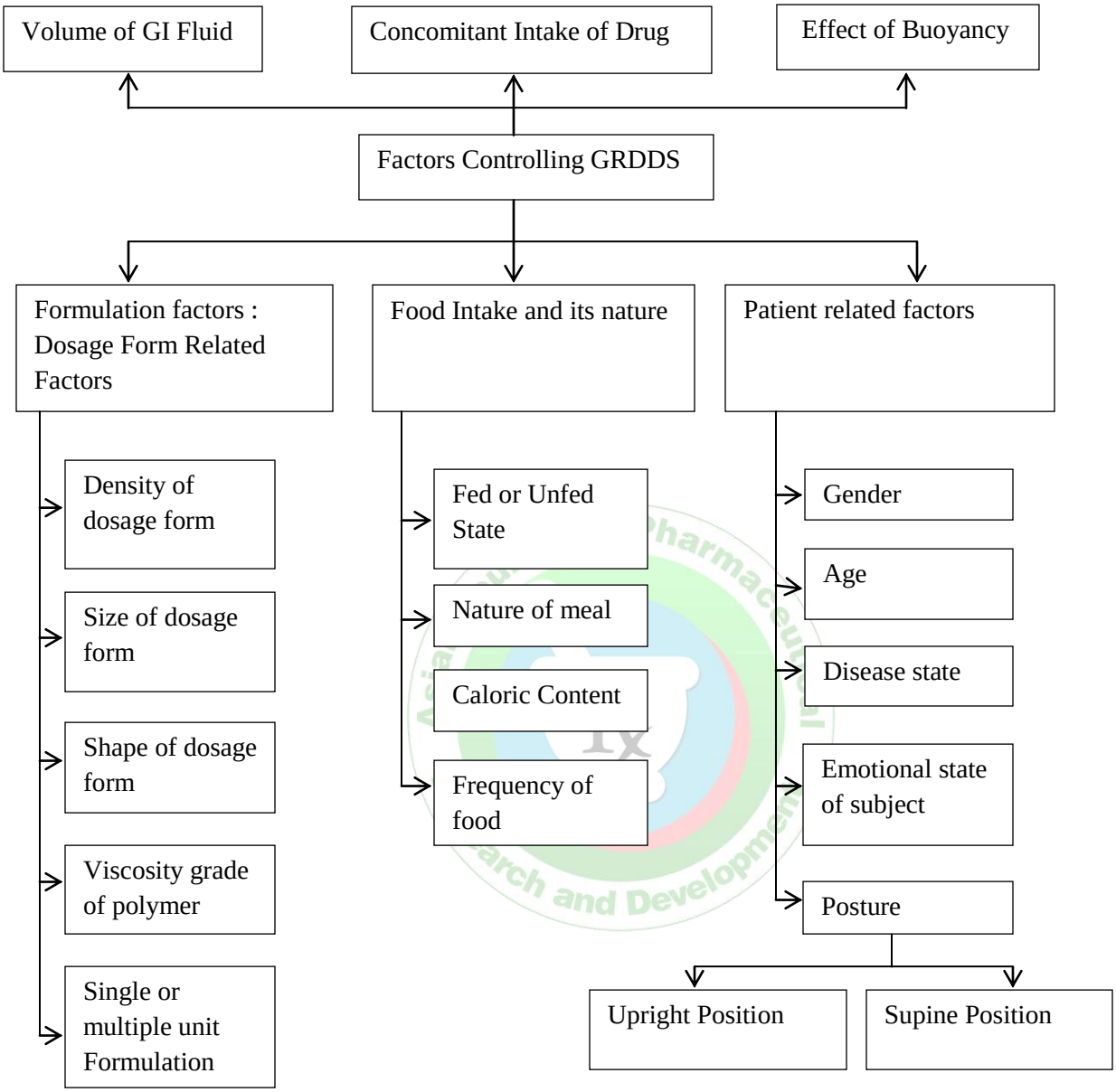

Figure No 18: Factors Controlling GRDDS

1. **Density:** Low density dosage forms might float to the top of the stomach's contents whereas high density dosage forms sink to the bottom. Less than 1.0 gm/cm³ of suitable density is required for floating property.
2. **Size:** Size should be more than 7.5 mm in diameter.
3. **Shape:** Either round or spherical shaped dosage form exhibit better property related to other shapes.
4. **Single or multiple unit formulation:** Multiple units are desirable due to foretell release profile.
5. **Fed or Unfed State:** Due to an increase in stomach motility, gastric retention time decreases during fasting conditions.
6. **Nature of Meal:** Variations in stomach motility cause a high concentration of fatty acids and other indigestible polymers to prolong the gastric retention time.
7. **Frequency of Feed:** Low frequency of migrating myoelectric complex (MMC) contributes to GRT upto 400 times which inturn depends on the frequency of food intake.

8. **Caloric Content:** A diet strong in protein and fat can raise GRT by 4 to 10 hours.
9. **Gender:** GRT is higher in men than in women.
10. **Age:** GRT is more prevalent in senior individuals and less prevalent in newborns and kids. Ages greater than 70 (>70) show longer GRT.
11. **Posture:** Between the patient's supine and upright ambulatory phases, GRT can change
12. **Disease State:** The GRT changes in people with gastric diseases such diabetes, chron's disease, hypothyroidism, hyperthyroidism, duodenal ulcers, etc.
13. **Concomitant Intake of Drug:** GRT is impacted when some medications are taken with Gastric motility enhancers or depressants.

Advantages of Gastro-retentive Drug Delivery Systems

1. Enhanced bioavailability

The bioavailability of riboflavin CR-GRDF is much higher than that of non-GRDF CR polymeric formulations. There are various processes associated to medication absorption and transit in the gastrointestinal system that function in concert to determine the magnitude of drug absorption[30].

2. Enhanced first-pass biotransformation

The pre-systemic metabolism of the tested compound may be significantly increased when the drug is presented to the metabolic enzymes (cytochrome P450, specifically CYP3A4) in a sustained way as opposed to by a bolus input, similar to the increased efficacy of active transporters with capacity limited activity[31].

3. Sustained drug delivery/reduced frequency of dosing

Sustained and slow input from CR-GRDF may result in flip-flop pharmacokinetics and permit lower dosing frequency for medicines with relatively short biological halflife. This trait is linked to increased patient compliance, which enhances therapy.

4. Targeted therapy for local ailments in the upper GIT

Prolonged and sustained medication administration from GRDF to the stomach may be useful for local therapy in the stomach and small intestine. Therapeutic medication concentrations can be achieved locally while systemic concentrations are modest as a result of drug absorption and distribution.

5. Reduced fluctuations of drug concentration

In comparison to instant release dosage forms, continuous drug input after CRGRDF treatment results in blood drug concentrations within a tighter range. As a result, oscillations in pharmacological effects are reduced, and concentration-dependent adverse effects associated with peak concentrations can be avoided. This property is especially important for medications with a limited therapeutic index[32].

6. Minimization of fluctuations in drug concentration

It enables the evoked pharmacological impact of medicines that activate different types of receptors at varying doses to be more selective.

7. **Reduced counter-activity of the body**

In many circumstances, the pharmaceutical response that interferes with the body's natural physiologic processes causes a rebound activity that reduces drug activity. Slow drug delivery into the body has been proven to reduce counter-activity, resulting in improved drug efficiency.

8. Extended time over critical (effective) concentration

For certain medications having non-concentration dependent pharmacodynamics, such as etalactam antibiotics, the clinical response is connected with the period of time over a key therapeutic concentration rather than the peak concentration. The sustained mode of administration allows for the prolonging of time above a critical concentration, which increases pharmacological effects and therapeutic results.

9. Minimized adverse activity at the colon

The drug's retention in the GRDF in the stomach reduces the amount of drug that reaches the colon. As a result, unwanted pharmacological actions in the colon may be avoided. The reason for GRDF formulation of beta-lactam antibiotics, which are only absorbed from the small intestine and whose presence in the colon results in the development of microbial resistance, is provided by this pharmacodynamic feature.

10. **Site specific drug delivery**

A floating dose form is a viable option, particularly for medicines with limited absorption sites in the upper small intestine[33]. Controlled, gradual drug administration to the stomach gives adequate local therapeutic levels while limiting systemic exposure to the drug. This lowers the adverse effects of the medication in the bloodstream. Furthermore, the increased gastrointestinal availability provided by a site-directed administration device may minimize dose frequency.

Disadvantages of Gastro-retentive Drug Delivery System [34]

Unsuitable for drugs with solubility or stability issues in the GI tract.

Drugs that irritate the stomach mucosa are likewise not appropriate.

The high turnover rate of gastric mucus poses significant challenges for bio adhesive systems, and irritants to the gastric mucosa are likewise unsuitable.

Drugs that absorb selectively in the colon, such as corticosteroids.

To float and perform efficiently, floating medicine delivery systems require a high fluid level in the stomach.

Unsuitable for medications that require an unstable, acidic environment, Erythromycin, for example.

Methods of Preparation of Gastro-Retentive Multiparticulate System

1. Solvent Evaporation Method

To construct the hollow inner core of a floating multiparticulate dosage form, solvent diffusion and evaporation processes can be used.The drug is either dissolved or disseminated in the polymer solution, which has been dissolved in an organic solvent. The medicine solution is then used to create oil in water emulsion by being emulsified into an aqueous phase with the proper ingredient (surfactants/polymer). After the formation of a stable emulsion, the organic solvent is evaporated either by raising the temperature under pressure or by constant stirring[35,36].The elimination of the solvent causes polymer precipitation at the oil/water interface of droplets, producing cavities and hollowing them out to give them floating qualities. For the development of such systems, polymers such as cellulose acetate, chitosan, Eudragit, Acrycoat, Methocil, polyacrylates, polyvinyl acetate, carbopol, agar, polyethylene oxide, and polycarbonates have been investigated[37].

2. Ionotropic Gelation Method

Ionotropic gelation is supported by poly electrolytes' capacity to cross link in the presence of opposing ions to form beads. The ionotropic gelation technique has become popular with the use of alginates, gellan gum, chitosan, and carboxymethyl cellulose for medication and cell encapsulation[38]. Despite having the property of coating on the drug core and acting as release rate retardants, natural poly electrolytes contain some anions in their chemical structure. By interacting with polyvalent cations, these anions create meshwork structures and promote gelation by attaching primarily to anion blocks. Dropping a drug-loaded polymeric solution into an aqueous solution comprising polyvalent cations yields the hydrogel beads[39].

3. Emulsion Solvent Diffusion Method

The affinity between the drug and the organic solvent is stronger in the emulsion solvent diffusion method than between the organic solvent and the aqueous solvent. Despite the fact that the organic solvent is miscible, the medication is dissolved in it and the solution is dispersed in the aqueous solvent, resulting in emulsion droplets. The organic solvent gradually diffuses out of the emulsion droplets into the surrounding aqueous phase, while the aqueous phase diffuses into the droplets that crystallise the medication.

4. **Novel Method for Foam Powder**

A novel multi-particulate gastroretentive drug delivery method based on low-density foam powder has also been presented and tested in vitro[40]. Floating microparticles were created using an oil-in-water solvent extraction / evaporation process using polypropylene foam powder, verapamil hydrochloride (as the model drug) and Eudragit RS, ethyl cellulose, or poly (methyl methacrylate). Methylene chloride was used to dissolve the medication and the polymer that controlled the release rate. Within this organic phase, polypropylene foam powder was then dissolved.The resultant suspension was then emulsified in an external aqueous poly (vinyl alcohol) solution and stirred to allow microparticleformulation.Themicroparticles were sieved, rinsed with water, and dried in a desiccator because they were irregular in shape and highly porous. Importantly, the drug encapsulation efficiency was high and nearly independent of the system's theoretical loading. Good in-vitro floating behaviour was seen in all cases. Surprisingly, the examined compositions produced a wide range of release patterns. Further research focused on the creation of a better production procedure for this sort of low density, foam-based, floating microparticle, as well as the demonstration of the system's in vitro performance[41]. The proposed innovative preparation technique has several advantages, including quick processing periods, no exposure of the materials to high temperatures, the opportunity to avoid harmful organic solvents, and high encapsulation efficiencies. Floating microparticles were made by soaking microporous foam particles in an organic solution of the drug and polymer, followed by drying[42].In most cases, good in-vitro floating behaviour was observed, and a wide range of drug release patterns could be created by altering the drug loading and type of second polymer[43].

5. Melt Granulation Technique

Melt granulation is a method that produces granules by adding either a molten binder or a solid binder that melts throughout the operation. This is also known as melt agglomeration or thermoplastic granulation[44,45,46,47].

Principle of Melt granulation:

The process of granulation consists of a combination of three phases:

a. Wetting and nucleation,

Wetting and Nucleation process

During the nucleation process, the binder comes into contact with the powder bed, resulting in the production of tiny agglomerates. mSchafer and Mathiesen propose two nucleation mechanisms.

Immersion

When the size of the molten binder droplets is larger than that of the small solid particles, nucleation by immersion takes place.

Fine solid particles are deposited onto the surfaces of molten binder droplets as immersion progresses.

Distribution

A molten binding liquid is applied to the surfaces of tiny solid particles using the distribution method.

The collision of the wetted particles produces the nuclei.

Small binder droplet size, low binder viscosity, and large shearing pressures are often favourable circumstances for nucleation via the distribution approach.

b. **Coalescence step**

In order to increase the success of fusion nuclei, it involves nuclei with leftover surface liquid.

The surface liquid gives the nuclei plasticity and is necessary for the nuclei's surface to deform for coalescence as well as to facilitate granulation rounding.

c. Attrition and breakage

Attrition and breakage are granulation fragmentation phenomena that are solidified by tray cooling to ambient temperature without the need for tumbling drying.

As a result, breaking is known to play a more important role in influencing the final parameters of the melt granulation during the granulation phase.

Requirements of Melt granulation

In general, a meltable binder concentration of 10-30% w/w in comparison to fine solid particles is utilised.

A meltable binder suited for granulation has a melting point that is typically between 50-100°C

Hydrophilic meltable binders are employed in the preparation of immediate-release dosage forms, whereas hydrophobic meltable binders are preferred in the preparation of prolonged-release formulations.

Fine solid particle melting points should be at least 20°C higher than the maximum processing temperature.

6. Meltable Binders

Its physical and chemical stability. It must be solid at room temperature and melt between 40 and 80°C.

Its hydrophilic-lipophilic balance (HLB) ensures proper active ingredient release.

There are two type of Meltable binder:

a) Hydrophilic meltable binders

b) Hydrophobic meltable binder

Polymeric Materials InGastroretentive Formulations

1. Hydroxypropylmethyl Cellulose (HPMC)

Hydroxypropyl methylcellulose (HPMC) is the most widely utilised hydrophilic carrier material in the manufacture of oral controlled drug delivery systems[48]. One or more of the three hydroxyl groups from the cellulose glucopyranose units have been changed in HPMC, commonly known as hypromellose, a cellulose ether, creating ether bonds. 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[49] . The most often used marketed HPMC is sold under the brand names Methocel® and Pharmacoat®.

2. 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 technologies due to its low Tg, indicating that the formulations may be treated at a low temperature. HPC has demonstrated the potential to create bioadhesive films[50] . The effect of different additives on the bioadhesive properties of HPC-based films was investigated, and it was discovered that incorporating Carbomer 971P and a polycarbophil into HPC films significantly improved bioadhesion when compared to the film containing HPC and PEG 3350.

Hydroxyethyl cellulose (HEC) is used as a gelling and thickening ingredient in the creation of biostructures for the delivery of hydrophobic medicines. Enalaprilmucoadhesive films, for example, were created using combinations of HEC and sodium carboxymethylcellulose and shown beneficial swelling characteristics as well as regulated drug release [51]. Hydroxyethyl cellulose (HEC), like HPC, has been added in multicomponent polymeric matrices to give the required gastro-retentive characteristics. Pentoxifylline effervescent floating tablets have been produced successfully employing sodium bicarbonate as a gas-forming agent and a polymeric matrix of sodium alginate and HEC, for example.

3. Carboxymethyl cellulose (CMC)

Carboxymethyl cellulose (CMC) is a semisynthetic, non-toxic, water-soluble cellulose derivative that contains carboxymethyl groups (-CH2-COOH) connected by an ether bond to some of the hydroxyl groups of the cellulose backbone's glucopyranose repeating units. Because the carboxylate groups in NaCMC are anionic, interactions with nonionic hydrocolloids such as HPMC and HEC may increase their gel-viscosity properties [51].

4. **Natural Gums**

Natural polymers, in addition to manufactured cellulose ethers, have been employed as hydrocolloids to successfully control drug release from swellablesystems[52] . Natural polymers contain beneficial properties such as biocompatibility and safety, and so have valuable pharmaceutical and biological applications. Natural gums—gellan gum, guar gum, carrageenans, and xanthan gum—along with other polysaccharides like alginates and chitosan and natural polymers like pectin and gelatin —are natural hydrocolloids or gel-forming agents that can swell in contact with gastric fluid, maintain relative shape integrity, and have a bulk density less than the gastric content[53,49].

5. Guar gum

Guar gum is a polysaccharide derived from the seeds of Cymopsistetragonolobus (Leguminosae family). Due to the dual composition of guar gum: an approximately 85 percent water-soluble fraction known as Guaran and an insoluble component, it swells quickly in the presence of water with a translucent suspension. The addition of borate ions to hydrated guar gum forms cohesive structural gels due to the mannose units[49] . When employed in solid dosage forms, guar gum enhances viscosity and works as a disintegrant and binder in the pharmaceutical industry[53].

6. **Carrageenans**

Carrageenans are anionic polysaccharides with a high molecular weight generated from Rhodophyceae red seaweeds. Because of their high durability, good 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. Notably, the carrageenans' actual density measurements were found to be

much greater than those of the cellulose ethers (MC, HPMC, NaCMC, and HPC)[53].

7. **Gellan Gum**

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

8. **Xanthan Gum**

Because it is non-toxic and non-irritant, xanthan gum is used in food, cosmetics, and topical and oral medicinal formulations. Its presence influences the zero-order kinetics of drug release from formulations [54].

9. **Crosslinkedpolyacrylates: Carbomers, Carbopol® and Polycarbophyl (PCP)**

Carbomers are high-molecular-weight synthetic polyacrylic acids that are cross-linked with polyalcohol allyl ethers such as pentaerythritolpolyallylether and polyallyl sucrose. Carbopol® polymer grades differ in terms of physical structure and chemical composition, crosslink density, polymerization solvent, crosslinking type, network electrical charge, and physical appearance, and thus in terms of performance. Carbomers require polymer ratios of 3 to 30% when used as controlled release polymers in matrix tablets. Carbopol and polycarbophil hydrogels are generally extremely permeable to a wide range of pharmacological substances and can be designed to "swell," releasing entrapped molecules via their network-like Structure[55,56]. The drug release can be fine-tuned by altering the polymer concentration.

10. Poly(ethylene oxide)(PEO)

High molecular weight PEO has been effectively used in controlled release dosage forms because the rate of swelling and erosion of the polymer allows for sustained release of APIs. High molecular weight PEO is viscoelastic in its swollen state because it can form dense polymeric networks in aqueous environments [57]. PEO is thus relevant as an additive for improving the mechanical properties of highly swellable and mechanically strong matrix tablets.

11. **Kollidon® SR**

Kollidon® SR is a poly(vinyl acetate) (PVAc) and povidone (poly(N-vinyl pyrrolidone) (PVP) mixture used largely as a matrix retarding agent. It is ideal for direct compression or hot melt extrusion of pH-independent sustained-release matrix tablets. PVAc is a polymeric material that, even when subjected to low compression pressures, forms a cohesive matrix. When the tablets are dissolved in stomach or intestinal fluid, the water-soluble PVP is leached out, resulting in holes through which the active ingredient slowly diffuses. Kollidon® SR is drug compound inert, and its sustained-release properties are unaffected by ions or salts because it lacks ionic groups [58,59].

Evaluation of gastro-retentive dosage form

1. Buoyancy Lag Time-

It is determined in order to assess the time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test.

2. **Specific Gravity / Density**- The displacement method, using Benzene as the displacement medium, can be used to calculate density.

3. **Resultant Weight**-The two fundamental factors that define buoyancy are bulk density and floating time. However, a single measurement of density is insufficient to fully represent buoyancy since density varies over time as a function of changes in the resulting weight. For example, a matrix tablet containing bicarbonate and a matrixing polymer initially floats due to gas production and entrapment, but after some time, a certain drug is released and at the same time, some of the matrixing polymer's outer layer may erode away, changing the dosage form's final weight.

4. Swelling systems

Swelling Index-The dosage form is taken from the SGF at regular intervals after being immersed in a swelling solution at 37°C, and dimensional changes are measured as an increase in tablet thickness or diameter with time.

Water Uptake- It is an indirect measurement of swelling property of swellable matrix. Here dosage form is removed out at regular interval and weight changes are determined with respect to time. Water uptake = WU = (Wt – Wo) * 100 / Wo

Where, Wt = weight of dosage form at time t.

Wo = initial weight of dosage form[60].

5. Particle Size and Shape

In comparison to light microscopy (LM), scanning electron microscopy (SEM) delivers better resolution. The most common methods for visualising microparticles are light microscopy (LM) and scanning electron microscopy (SEM). Both are capable of determining the shape and exterior structure of a multiparticulate. In the case of double-walled microspheres, LM allows for control over coating settings. Before and after coating, the Multiparticulate formations can be seen and measured microscopically. SEM can investigate multiparticular surfaces, and after particles are cross sectioned, it can also investigate double walled systems. Conflocal fluorescence microscopy is used to characterise the structure of multiple walled microspheres. Other than instrumental approaches, laser light scattering and multi size coulter counter can be employed to characterise the size, shape, and morphology of the Multiparticulate[61].

6. Entrapment Efficiency -

By allowing washed multiparticulate to lyse, the multiparticulate's capture effectiveness or the percent entrapment can be calculated. The active ingredients of the lysate are then determined in accordance with the requirements of the monograph. Equation is used to calculate the percent encapsulation efficiency.

% Entrapment = Actual content/Theoretical content x 100

7. Floating Behavior-

In 100 ml of the simulated gastric fluid (SGF, pH 2.0), the appropriate amount of the floating microparticulate is added, and the mixture is agitated using a magnetic stirrer. Filtration is used to remove the layer of buoyant microparticulate after pipetting. Filtration separates the particles in the sinking particulate layer. Both kinds of particles are dried in a desiccator until they have a constant weight. Both microsphere fractions are weighed, and the weight ratio of the floating particles to the total of the floating and sinking particles is used to calculate buoyancy.

Buoyancy (%) = Wf / Wf + Ws.

Where, Wf and Ws are the weights of the floating and settled microparticles [62].

8. In Vitro Release Studies

In a dissolution apparatus, the rate of release of floating microparticulate is determined. A weighted amount of floating microspheres equal to the medicine dose is taken and placed in the dissolving rate apparatus basket. During the drug release research, the dissolving fluid is kept at 37 ± 0.5°C with a rotation speed that produces sink conditions [63].

9. Drug – Excipient interaction study

FT-IR spectroscopy, differential scanning calorimetry, and high performance liquid chromatography can be used to investigate it.

10. In vivo Evaluation Test

a. Radiology X-ray is widely used for examination of internal body systems. Barium Sulphate is widely used Radio Opaque Marker.

b. Scintigraphy emitting substances are incorporated into dosage forms, much like with X-rays, and then images are captured using scintigraphy. Widely used emitting material is 99Tc[64]

c. Gastroscopy peroral endoscopy using fibre optics or video technologies is known as gastroscopy. The use of gastroscopy allows for a visual examination of the effects of stomach extension[65].

d. Magnetic Marker Monitoring This method uses an iron powder-filled dosage form that is magnetically marked so that images can be captured by highly sensitive biomagnetic measurement equipment. Advantage of this method is that it is radiation less and so not hazardous.

e. Ultrasonography used sometimes, not used generally because it is not traceable at intestine.

f. 13C Octanoic Acid Breath Test 13C Octanoic acid is incorporated into GRDDs. In stomach due to chemical reaction, octanoic acid liberates CO2 gas which comes out in breath. The 13C isotope takes the place of the significant Carbon atom that will be present in CO2. Therefore, the length of time that 13CO2 gas remains in the breath can be regarded as the dose form's stomach retention period. No reaction takes place, and no CO2 is released while the dose form travels to the colon. Consequently, this approach is less expensive than others.

Comparsion between Conventional and Gastroretentive Drug Delivery System [34]

Table No 2: Comparsion between Conventional and Gastro-retentive Drug Delivery System

Sr. no	Parameter	CDDS	GRDDS
1	Toxicity	High risk of toxicity	Low risk of toxicity
2	Patient Compliance	Less	Improves patient compliance
3	Drug with narrow absorption window in small intestine	Not suitable	Suitable
4	Drug acting locally in the stomach	Not much advantageous	Very much advantageous
5	Drugs having rapid absorption through GIT	Not much advantageous	Very much advantages
6	Drugs which degrades into colon	Not much advantageous	Very much advantages
7	Drugs which are poorly soluble at an alkaline pH	Not much advantageous	Very much advantages
8	Dose dumping	High risk of dose dumping	No risk of dose dumping
9	Drug	**Beneficial for drugs-** That have rapid GI absorption Degrade in colon That show local action in the stomach	**Not beneficial for drug –** That have low GI absorption Degrade in colon That show local action in the stomach

CONCLUSION

The oral drug administration route is the most common since it is straightforward to utilise. The stomach and intestines are where oral medications are primarily absorbed. Gastro-Retentive Drug Delivery System (GRDDS), a drug delivery system that can prolong the contact period with the stomach, is therefore necessary. A long-term drug delivery system that can retain drugs in the stomach for extended periods of time is the GRDDS. GRDDS has the power to boost bioavailability, improve the solubility of drugs that aren't very soluble in alkaline solutions, regulate therapeutic levels to prevent fluctuations, and lengthen the half-life to reduce the need for repeated dosing.

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