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GASTRORETENTIVE FLOATING DRUG DELIVERY SYSTEM DISADVANTAGES PREVENTION

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ABSTRACT

In recent years, particularly in the last two decades a great deal of technologies

scientific research hes been devoted to development of controlled oral drug delivery system to overcome physiological problems the greateric emplying times[GET] in order to able to formulate gastro retentive dosage forms which allow the delivery of restricted absorption drugs which are absorbed in particular partition of GIT tract. Several advantages and disadvantages are impact on the GI tract.Overall the advantages of GRDDS outweight the disadvantage , and ongoing research and development are addressing the challenges associated with these systems.To prevent these disadvantages there are several approaches like

1. Minimize the 1st pass metabolism the strategies to prevent chemical modifications [prodrug,lipid,solubility,molecular size] prokinetic enhances [cyp inhibitors,effector] formulations strategies sustained released formulatives

2. To enhance the solubility strategies formulation PH control,solubuling agents,solids dispersion,chemical modification salt formation derivitization.

3. To prevent gastric irritation:-formulation strategies Enteric coating,floating adhesive mucoadhesive system

4. To prevent [or] to overcome this limitations[solubility,enhancement,crystol engineering, use of surfactants co solvents systems.

5. To prevent increase formation cost in gastro retentive floating[optimize formulation composition,cost effective drug loading methods.

6. To prevent salivation&swallowing during drug delivery[salivation prevention,swallowing prevention,mucoadhesive system,gastro retentive controlled release..

In this review the current and recent developments of FDDS including patented,generic,new technologies & manufacturing processing & marketed products are mentioned in this article.

KEYWORDS:-Gastro retentive drug delivery system , cyp inhibitors,Enteric coating , Floating adhesive,Mucoadhesive, crystol engineering, salivation prevent.

INTRODUCTION

GASTRORETENTIVE FLOATING DRUG DELIVERY SYSTEM

While oral drug delivery systems offer many benefits, including high patient compliance, costeffectiveness, ease of storage and transportation, formulation flexibility, and simplicity of administration, methods face several obstacles because of the gastrointestinal tract's heterogeneity, bacterial PH, the dosage form's stomach retention time, surface area, and enzymatic activity.GRDDS is a kind of drug delivery system that is intended to extend the halflife of a medication in the stomach [1].

Because oral dose forms are so simple to administer and handle, patients are highly compliant with taking them. Even while oral controlled drug delivery has advanced significantly over the past 20 years, it has not been very effective when it comes to medications that have a narrow window for absorption throughout the gastrointestinal tract (GIT).

Changing the GI transit time is one of the biggest challenges in developing an oral controlled drug delivery system. The gastric emptying of pharmaceuticals varies greatly and depends on the dosage form and the stomach's fed/fasted state. Normal gastric residence times typically fall between 5 minutes and 2 hours. In the fasted state, the electrical activity in the stomach, known as the inter-digestive myoelectric cycle or migrating myoelectric complex (MMC), controls the activity and, consequently, the transit of dosage forms. It is divided into four phases.

Phase 1: No contraction period (40–60 min]

Phase 2: Intermittent contraction period (20–40 minutes)

Phase 3: The housekeeping wave, which is a period of consistent contractions at the maximum frequency that travels distally (10–20 min)

Phase 4: The interval of time between Phase I and Phase III (0–5 minutes)

If there are physiological issues and other variables, such as the availability of food, gastric emptying might be unpredictable. Short-half-life medications are rapidly removed from the bloodstream circulation. To get around these issues and distribute the medication in a way that keeps its plasma concentration stable for a longer amount of time, several oral controlled delivery systems have been developed.[2]

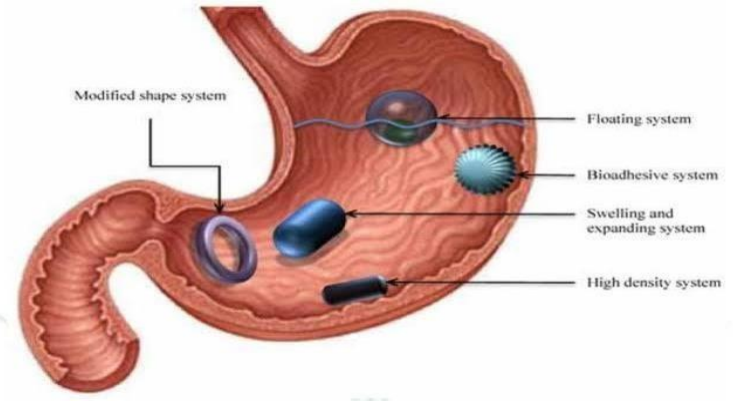

Figure 1: The Need for a Gastro Retentive Drug Delivery System

Medication absorbed from the gastrointestinal tract's proximal region (GIT) medications that are less soluble or that are broken down by the alkaline pH they come into contact with in the lower gastrointestinal tract. medications that are absorbed as a result of fluctuating stomach emptying time.

To treat certain disorders, drugs can be delivered locally or continuously to the stomach and proximal small intestine. very helpful in treating peptic ulcers brought on by H. Pylori infections.[3, 4]

Methods for treating gastric retention

A number of strategies have been tried to improve the retention of an oral dose form in the stomach. One such strategy is the bioadhesive strategy, which applies a polymer with glycoprotein's adhesive properties near to the stomach's epithelial surface. Other methods include of: approaches with high and low densities.

Approaches to gastric retentio Various approaches have been pursued to increase the retention of an oral dosage form in the stomach, for example, bioadhesive approach in which the adhesive capacity of some polymer with glycoprotein is closely applied to the epithelial surface of stomach. Other approaches include: high density and low density approach.

1) High density approach

For preparing such type of formulations, the density of the pellets should be higher than the stomach fluid. It would be at least 1.50 G/ml. In this type, the drug can be coated or mixed with heavy, nontoxic materials such as barium sulfate, titanium dioxide, etc.

2) Low density approach

Floating systems come under low density approach. In this approach, the density of pellets should be less than 1 g/ml, so as to float the pellets or tablets in the gastric fluid

and, release the drug slowly for a longer period of time. This type is also called as Hydro dynamically balanced System (HBS).

FACTORS AFFECTING GASTRIC RETENTION

- Gastric retention time (GRT) is affected several factors including size and shape of dosage forms, density, intake of food and drugs such as anticholinergic agents, prokinetic agents and opiates.
- Biological factors which affect gastric emptying include age, gender, posture, body weight and disease state.
- For HBS dosage form to floating stomach it should have the density less than the gastric contents.
- Food has major effect on GRT dosage form by depending on its nature, caloric contents and the frequency of

intake which has major effect on gastric emptying than specific gravity.

- FDDS demonstrated that a GRT of four to ten hours could be achieved after a fat and protein meal[5]

Floating drug delivery:

FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate. After release of drug, the system is eliminated from the stomach. This results in an increased GRT and better control of fluctuations in plasma drug concentration. The floating sustained release dosage forms exhibit most of the characteristics of hydrophilic matrices and are known as 'hydrodynamically balanced systems (HBS) since they are able to maintain their low apparent density, while the polymer hydrates and builds a gel like barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (3–4 h) in the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents. Many studies have demonstrated the validity of the concept of buoyancy in terms of prolonged GRT of the floating forms, improved bioavailability of drugs and improved effects in clinical situations. The results obtained have also demonstrated that the presence of gastric contents is needed to allow the proper achievement of the buoyancy retention effect. Amongthe different hydrocolloids recommended for floating form formulations, cellulose ether polymers are the most popular, especially Hydroxypropyl methyl cellulose (HPMC). Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy. In parallel with formulation studies, investigations have been undertaken in animals and humans to evaluate the intragastric retention performance of floating forms. These assessments were carried out either indirectly through pharmacokinetic studies with a drug tracer, or directly by means of X-ray and gamma scintigraphic monitoring of the transit through the GI tract. When a floating capsule is administered to subjects who have consumed a fat and protein meal, it remains buoyant at the surface of the gastric contents in the upper part of the stomach and moves to the lower region progressively as the meal empties from the stomach. The reported gastric retention times range from 4 to 10 h. Pharmacokinetic and bioavailability evaluation studies confirm the favourable effect of this prolonged gastric residence time.[6]

Factors affecting FDDS:

Density: GRT is a function of dosage form buoyancy which is dependent on density.

Size: Dosage form units with a diameter more than 7.5 mm are reported to increase GRT compared with those with a diameter of 9.9mm.

Shape: Tetrahedron and ring-shaped devices with a flex ural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to exhibit a better GRT and 90%–100% retention at 24 h compared with other shapes.

Single or multiple unit formulations: Multiple unit formulations exhibit a more predictable release profiles and insignificant impairment of performance due to unit failures, allow coadministration of units with different release profiles or containing incompatible substances and permit a larger margin of safety with regard to dosage form

failure compared with single unit dosage forms.

Fed or fasted state: Under fasting conditions, the GI motility is characterised by periods of strong motoractivity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2
h. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

Nature of the meal: Consumption of indigestible polypolymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus reducing the gastric emptying rate and prolonging drug release.

Caloric content: GRT can be increased by 4 to 10 h with a meal that is high in proteins and fats

Frequency of feeding: The GRT can increase by over 400 min when successive meals are given with a single meal due to the low frequency of MMC

Gender: Mean ambulatory GRT in males (3.4± 0.6 h) is less compared with age and race matched females (4.6 ± 1.2 h), regardless of the weight, height and body surface area.

Age: Elderly people, especially those over 70, have a significantly longer GRT.

Posture: GRT can vary between supine and upright ambulatory patient states.

Concomitant drug administration: Anticholinergics, like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride, affect the FDDS.

Biological factors: Diabetes and Crohn's disease, also affect the FDD[7]

Mechanism of floating systems:

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gasgenerating systems and swelling or expanding systems), mucoadhesive systems, high- density systems, modified shape systems, gastric-emptying delaying devices and co- administration of gastric emptying delaying drugs. Among these, the floating dosage forms are the most commonly used. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is eliminated from the stomach. This results in an increased GRT and a better control of the

fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention effect, a minimal level of floating force (F) is also required to maintain the buoyance of the dosage form on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F(as a function of time)that is required to maintain a submerged object.The object floats better if F is on the higher positive side.

This apparatus helps in optimizing FDDS with respect to stability and sustainability of floating forces produced in order to prevent any unforeseeable variations in intragastric buoyancy[8] F

= Fbuoyancy – F gravity = (Df – Ds) g v

Where,

F= total vertical force, Df = fluid density,

Ds = object density, v = volume

g = acceleration due to gravity.

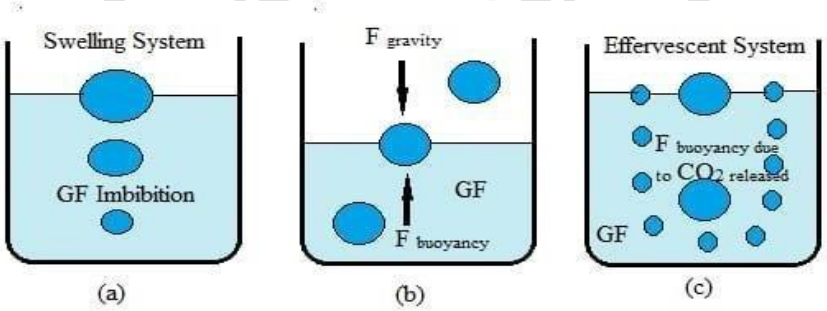

Figure 2- Mechanism of floating system

Based on the buoyancy mechanism, FDDS can be classified into:

1. single unit floating dosage systems
2. multiple unit floating dosage systems
3. raft forming systems

Single unit floating dosage system

Effervescent systems; Gastroretentive floating drug delivery system

These buoyant systems use matrices prepared with swellable polymers like HPMC, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that becomes a gas at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach.[9] Other

approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide.

when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with HPMC and floating systems based on ion exchange resin technology. The excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. Ozdemir et al[10] prepared floating bilayer tablets to achieve controlled release of furosemide. The low solubility of the drug could be enhanced by using the kneading method, preparing a solid dispersion with β cyclodextrin mixed in a 1: 1 ratio.

One layer contained the polymers HPMC4000, HPMC100, and CMC (for control of drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid. Radiographic studies on 6 healthy male volunteers showed that floating tablets were retained in the stomach for 6 h and further blood analysis studies showed that the bioavailability of these tablets was 1.8-fold greater than that of conventional tablets. On measuring the volume of urine passed, the peak diuretic effect seen with conventional tablets was reduced and prolonged in the case of the floating dosage form.

Penners et al[11] prepared an expandable tablet containing a mixture of polyvinyl lactams and polyacrylates that swelled rapidly in an aqueous environment and, thus, remained in the stomach over an extended period of time. In addition to this, gas-forming agents were also incorporated so that, as soon as the gas produced, the density of the system was reduced and, thus, the system tended to float on the gastric contents. Talwar et al[12] prepared a once-dailyformulation for oral administration of ciprofloxacin. The formulation was composed of 69.9% ciprofloxacin base, 0.34% sodium alginate, 1.03% xanthum gum, 13.7% sodium bicarbonate, and 12.1% cross-linked polyvinyl pyrrolidine. The cross linked PVP initially and the gelforming polymers later formed a hydrated gel matrix that entrapped the gas, causing the tablet to float and be retained in the stomach. The hydrated gel matrix created a[diffusion path for the drug, resulting in sustained release of the drug.

Baumgartner et al[13] prepared a matrix-floating tablet incorporating a high dose of freely soluble drug. The formulation containing 54.7% of drug, HPMC K4 M, Avicel PH 101, and a gas-generating agent gave the best results. It took 30 seconds to become buoyant. In vivo experiments with fasted beagle dogs showed a prolonged gastric residence time. A comparison of gastric motility and stomach emptying between humans and dogs showed no significant differences and, therefore, it appeared that the experimentally proven increased gastric residence time in beagle dogs could be compared with known literature values for humans, where this time is less than 2.h

Non-effervescent systems:

This type of system, after swallowing, swells unrestrained following the uptake of gastric fluid and so prevents the exit from the stomach. These systems may be referred to as ‘plug-type systems’ since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer renders these dosage forms buoyant. Examples of this type of FDDS include a colloidal

gel barrier,[14] microporous compartment system,[15] alginate beads[16] and hollow microspheres.[17]

Another type is a fluid- filled floating chamber[18] which includes incorporation of a gas-filled floatation chamber into a microporous component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug is retained. The fluid present could be air, under a partial vacuum, or any other suitable gas, liquid, or solid having an appropriate specific gravity and exhibiting inert behaviour. The device is of a size that can be easily swallowed, it remains afloat within thestomach for a prolonged time, and, after release is complete, the shell disintegrates, passes into the intestine, and is then eliminated.

A newer self-correcting floatable asymmetric configuration drug delivery system[19] has a 3layer matrix to control the drug release. This 3-layer principle has been improved by development of an asymmetric configuration drug delivery system in order to modulate the degree of release and achieve zero-order release kinetics by initially maintaining a constant area at the diffusing front with subsequent dissolution/erosion towards completion of the release process. This system was designed in such a manner that it floated to prolong the gastric residence time in vivo, resulting in a longer total transit time within the gastrointestinal tract with a maximum absorptive capacity and, consequently, greater bioavailability. This particular characteristic would be applicable to drugs that have pH-dependent solubility, a narrow window of absorption, and are absorbed by active transport from either the proximal or distal portion of the small intestine.

Yang et al[20] developed a swellable asymmetric triple-layer tablet with floating ability to prolong the gastric residence time of a triple drug regimen (tetracycline, metronidazole, and clarithromycin) for the treatment of Helicobacter pylori–associated peptic ulcers using HPMC and poly(ethylene oxide) (PEO) as the rate-controlling polymeric membrane excipients. The design of the delivery system was based on the swellable asymmetric triple-layer tablet approach. HPMC and poly (ethylene oxide) were the major rate-controlling polymeric excipients. Tetracycline and metronidazole were incorporated into the core layer of the triplelayer matrix for controlled delivery, while bismuth salt was included in one of the outer layers for instant release. Floatation was accomplished by incorporating a gas-generating layer consisting of sodium bicarbonate and calcium carbonate with swelleble polymers. Over 6–8 h of sustained delivery of tetracycline and metronidazole was achieved with this dosage form which was still floating at the end of this period.

Streubel et al[21] prepared single-unit floating tablets based on a polypropylene foam powder (Accurel MP 1000) and a matrix-forming polymer. The highly porous foam powder in the matrix tablets provided a density much lower than the density of the release medium. Varying the ratios of the matrix-forming polymers and the foam powder allowed the drug release patterns to be modified as required.

Sheth and Tossounian developed hydrodynamically balanced sustained release tablets containing drug and hydrophilic hydrocolloids, which, on contact with gastric fluids at body

temperature, formed a soft gelatinous mass on the surface of the tablet resulting in a waterimpermeable colloid gel barrier on the surface The drug was slowly released from the surface of the gelatinous mass that remained

buoyant on the gastric fluid.

Wu et al[22] prepared floating sustained release tablets of nimodipine using HPMC and PEG6000. Prior to formulation of the floating tablets, nimodipine was incorporated into a poloxamer-188 solid dispersion after which it was directly compressed into floating tablets. It was found that increasing the HPMC and decreasing the PEG 6000 content resulted in a decline in the in-vitro release of nimodipine.

Nur and Zhang[23] prepared floating tablets of captopril using HPMC (4000 and 15000 cps) and carbopol 934P. They concluded that the buoyancy of the tablets was governed by both the swelling of the hydrocolloid particles on the tablet surface when they came in to contact with the gastric fluids and the presence of internal voids in the centre of the tablets (porosity). A prolonged release from these floating tablets was observed, compared with the conventional tablets, and a 24-h controlled release of captopril from the dosage form was achieved.

Single-unit formulations are associated with problems such as sticking to one another or obstruction in the gastrointestinal tract, which may result in local irritation. The main drawback of such systems is the “all or none” phenomenon. In such cases there is a danger of the dosage form passing into the intestine when of house-keeper waves are produced. Multiple unit dosage forms have been designed to overcome this problem.

Multiple unit floating systems: In spite of extensive research and development in the area of HBS and other floating tablets, these systems suffer from an important drawback of high variability of the gastrointestinal transit time, when orally administered, because of their allor- nothing gastric emptying nature. In order to overcome this, multiple unit floating systems were developed, which reduce the inter-subject variability in absorption and lower the probability of dose-dumping. Reports have described the development of both noneffervescent and effervescent multiple unit systems. Much research has been focussed on and investigators are still exploring the field of hollow microspheres, capable of floating on the gastric fluid, and having improved gastric retention properties.

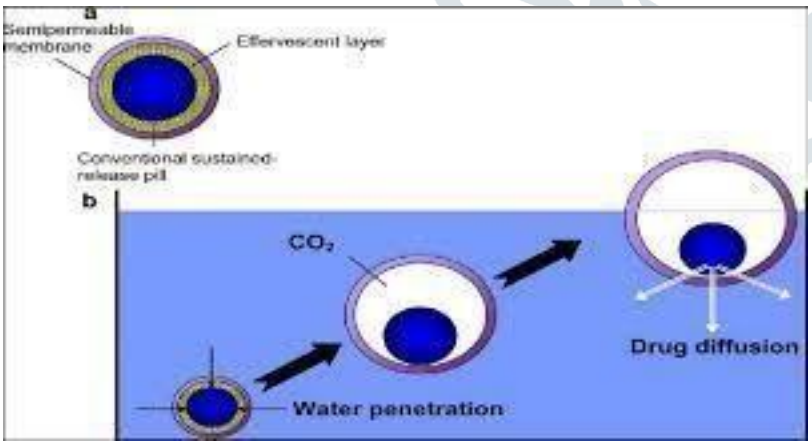

Figure 3- Multiple Unit Floating System

Non effervescent system

There are few reports in the literature on non effervescent multiple unit systems, compared with effervescent systems. However, some workers have reported the possibility of developing such a system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion has been reported.[24] A mixture of drug, chitosan and acetic acid is extruded

through a needle, and the extrudate is cut and dried. Chitosan hydrates and floats in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio.

Effervescent systems (gas-generating systems):

Ikura et al[25] described sustained release floating granules containing tetracycline hydrochloride. The granules are a mixture of drug granulates of two stages A and B, in which A contains 60 parts of HPMC, 40 parts of polydacrylic acid and 20 parts of drug and B contains 70 parts of sodium bicarbonate and 30 parts of tartaric acid. Sixty parts by weight of granules of stage A and 30 parts by weight of granules of stage B are mixed along with a lubricant and filled into capsules. In dissolution media, the capsule shell dissolves and liberates the granules, which have a floating time of more than 8 h and a sustained drug release of 80% in about 6.5
h. Floating minicapsules of pepstatin having a diameter of 0.1–0.2 mm have been described by Umezawa[26]These minicapsules contain a central core and a coating. The central core consists of granules composed of sodium bicarbonate, lactose and a binder, which is coated with HPMC. Pepstatin is coated on the top of the HPMC layer. The system floats because of the
CO2 released in gastric fluid and the pepstatin remains in the stomach for prolonged period. Alginates have also received much attention in the development of multiple unit systems. Alginates are non-toxic, biodegradable linear copolymers composed of L-glucuronic andLmannuronic acid residues. A multiple unit system prepared by Iannuccelli et al[27] consists of a calcium alginate core and a calcium alginate/PVA membrane, both separated by an air compartment. In the presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. An increase in the molecular weight and the concentration of PVA, resulted in enhancement of the floating properties of the system. Freeze-drying has also been reported for the preparation of floating calcium alginate beads.[28] Sodium alginate solution is added drop-wise to an aqueous solution of calcium chloride, causing instant gel of the droplet surface, due to the formation of calcium alginate. The obtained beads are freeze-dried resulting in a porous structure, which aids floating. The authors studied the behaviour of radiolabeled floating beads and compared them with nonfloating beads in human volunteers using gamma scintigraphy. A prolonged gastric residence time of more than 5.5 h was observed for floating beads. The nonfloating beads had a shorter residence time with a mean onset emptying time of 1 h.

Ichikawa et al[29] developed a new multiple type of floating dosage system having a pill in the core, composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of the effervescent agents containing sodium bicarbonate and tartaric acid was divided into two sublayers to avoid direct contact between the two agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in buffer at 37˚C, it settled and the solution permeated into the effervescent layer through the outer swellable membrane. Then CO2 was generated by the neutralization reaction between the two effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/ml[30,31].

Drugs used in the floating dosage forms:

Floating microspheres: Aspirin, griseofulvin, pnitroaniline, ibuprofen, ketoprofen,[32] piroxicam, verapamil, cholestyramine, theophylline, nifedipine, nicardipine, dipyridamol, tranilast[33] and terfinadine[34]

Floating granules: Diclofenac sodium, indomethacin and prednisolone.

Films: Cinnarizine[35], albendazole.

Floating tablets and pills: Acetaminophen, acetylsalicylic acid, ampicillin, amoxycillin trihydrate, atenolol, fluorouracil, isosorbide mononitrate,[36].

Advantages[37]

- **Enhanced Bioavailability:** GRDDS prolong the residence ti me of drugs in the stomach, allowing for controlled and sustained release. This can enhance the absorption of drugs with limited solubility or those requiring specific conditions for optimal uptake.

- **Improved Therapeutic Efficacy:** The controlled release provided by GRDDS helps maintain therapeutic drug levels in the body over an extended period. This can lead to more consistent pharmacological effects, reducing fluctuations in drug concentration and improving overall therapeutic efficacy.

- **Reduced Variability in Plasma Drug Levels:** GRDDS minimize fluctuations in drug concentration, providing amore predictable and sustained release profile. This is particularly advantageous for drugs with a narrow therapeutic window, where maintaining consistent plasma levels is critical for safety and efficacy

- **Targeted Drug Delivery:** GRDDS can be designed to release drugs at specific locations in the gastrointestinal tract. This targeted delivery is beneficial for drugs that are absorbed in particular regions, leading to localized therapeutic effects.

- **Patient Compliance:** The prolonged release offered by GRDDS often allows for less frequent dosing, improving patient compliance and convenience. Reduced dosing frequency can contribute to better adherence to treatment regimens.

- **Treatment of Gastrointestinal Conditions:** GRDDS are particularly useful for drugs treating conditions within the gastrointestinal tract, such as peptic ulcers or inflammatory bowel diseases. By ensuring prolonged contact with the affected area, these systems enhance the therapeutic effectiveness of such drugs.

- **Minimization of Side Effects:** Controlled release can help minimize side effects associated with high peak concentrations of drugs. By maintaining drug levels within the therapeutic range, GRDDS may reduce the likelihood of adverse reactions.

- **Flexibility in Formulation:** GRDDS offer flexibility in formulation design, allowing for the incorporation of various mechanisms such as floating, bioadhesion, or expansion. This adaptability enables the optimization of drug delivery based on the specific characteristics of the drug and the desired therapeutic outcomes.

- **Potential for Localized Treatment:** GRDDS can be tailored for localized drug delivery, allowing for focused treatment of specific areas within the gastrointestinal tract. This is advantageous for diseases or conditions that primarily affect localized regions.

- **Optimization of Drug Therapy for Individual Patients:** The customization potential of GRDDS allows

for tailoring drug delivery to individual patient needs, promoting personalized medicine approaches and optimizing therapeutic outcomes.

- Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide

- Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels. e.g. b-lactam antibiotics (penicillins and cephalosporins)

- Retention of drug delivery systems in the stomach prolongs overall.

- Gastrointestinal transit time thereby increasing bioavailability of sustained release delivery systems intended for once-a-day administration.

COMPARISON BETWEEN CONVENTIONAL DDS AND GASTRORETENTIVE DDS

Conventional Drug Delivery Systems[GRDDS]	Gastroretentive Drug Delivery Systems (GRDDS)
1.Gastric Transit Time: Conventional systems do not specifically target or control gastric transit time.Rapid transit through the stomach may limit drug absorption, especially for drugs requiring sustained release or those with specific absorption sites.	**1.Gastric Transit Time:** GRDDS are designed to prolong gastric residence time, ensuring that the drug remains in the stomach for an extended period.Targeted delivery to the upper gastrointestinal tract allows for optimal drug absorption.
2.Drug Release: Release patterns are typically not tailored to the physiological conditions of the gastrointestinal tract. Drug release may occur in various segments of the gastrointestinal tract, leading to unpredictable absorption profiles.	**2.Drug Release:** GRDDS offer controlled and sustained drug release, often tailored to the specific physiological conditions of the stomach.The release profile is optimized for improved bioavailability and therapeutic efficacy.

3. **Bioavailability:** Variability in drug absorption may occur due to factors such as gastric emptying rate and the presence of food, impacting overall bioavailability. Limited bioavailability may result in the need for higher doses or more frequent administration. 4. **Retention Mechanisms:** Rely on normal gastrointestinal transit for drug delivery. Lack specific mechanisms for prolonged retention in the stomach.	3. **Bioavailability:** Enhanced bioavailability is a key advantage of GRDDS due to the controlled release and prolonged residence time in the stomach. The predictability of drug absorption can lead to improved therapeutic outcomes and reduced variability. 4. **Retention Mechanisms:** Utilize various mechanisms such as buoyancy, bio adhesion, expansion, or high-density formulation to achieve prolonged gastric retention. These mechanisms ensure that the dosage form remains in the stomach, facilitating controlled drug release

DISADVANTAGES

Drugs undergoing significant first-pass metabolism can be challenging. Drugs with limited acid solubility can be challenging.

- For drugs that cause gastric lession or irritation is crucial
- Not suitable for drugs that have solubilty or stability problems in GIT.
- Drugs which are irritant to gastric mucosa are also not suitable.
- Salivation salvation in GRDDS.
- Movement affects mucosa adhessive system.
- The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- Not suitable for drugs that have solubility or stability problem in GIT.
- GRDDS, as their performance relies on predictable gastric residence times. Influence of Food: The presence of food in the stomach can affect the performance of GRDDS. Food intake may alter gastric emptying rates, potentially leading to inconsistent drug release and absorption.
- **Formulation Complexity:** Designing effective GRDDS often requires sophisticated formulation technique which can ,which can increase the complexity and cost of drug development. Achieving the desired balance of buoyancy, bioadhesion, or expansion while maintaining stability and safety is a challenging tasking.
- **Potential for Incomplete Gastric Emptying:** In some cases, GRDDS may not completely empty from the stomach, leading to the possibility of accumulation and potential complications. Incomplete gastric emptying

could affect subsequent drug doses and may pose a risk of overdose.

❖ **Gastrointestinal Irritation:** Some formulations of GRDDS, particularly those using bioadhesive mechanisms, may pose a risk of irritation to the gastrointestinal mucosa. Prolonged contact with the gastric lining may lead to localized irritation or inflammation.

❖ **Limited Applicability to All Drugs:** Not all drugs are suitable candidates for GRDDS. Some drugs may not benefit from prolonged residence in the stomach, and the formulation may not be compatible with the drug's physico chemical properties.

❖ **Potential for Incomplete Drug Release:** Factors such as the variability in gastric pH, gastric motility, and the presence of food can influence the release of of drugs from GRDDS. This variability may lead to incomplete drug release and affect therapeutic outcomes.

❖ **Patient Acceptance and Compliance:** The need for patients is to understand and follow specific administration. instructions for GRDDS may pose challenges to acceptance and compliance.Patients may find it challenging to adhere to specific dosing requirements,impacting the effectiveness of treatment.[38, 39 ,40 ,41]

PREVENTION OF DISADVANTAGES:

1. Drugs undergoing significant first-pass metabolism can be challenging. Here are some strategies to prevent or minimize first-pass metabolism:[42]

Chemical Modifications:

1. **Prodrugs:** Design prodrugs that are converted to active drugs after absorption.
2. **Lipid solubility**: Increase lipid solubility to enhance absorption.
3. **Molecular size:** Reduce molecular size to decrease hepatic extraction.

Pharmacokinetic Enhancers:

1. **CYP inhibitors:** Co-administer drugs that inhibit cytochrome P450 (CYP) enzymes.
2. **Efflux inhibitors:** Use drugs that inhibit efflux transporters (e.g., P-glycoprotein).
3. **Absorption enhancers**: Add excipients that enhance absorption (e.g., surfactants).

Formulation Strategies:

1. **Sustained-release formulations:** Reduce peak concentrations and prolong absorption.
2. **Controlled-release formulations**: Regulate drug release to minimize hepatic exposure.
3. **Liposomes:** Encapsulate drugs in liposomes for targeted delivery.

Route of Administration:

1. **Sublingual:** Bypass hepatic circulation via sublingual absorption.

2. **Transdermal:** Use skin patches to avoid first-pass metabolism.
3. **Rectal:** Administer drugs rectally to partially bypass liver metabolism

Specific Examples:

1. Caffeine (oral bioavailability: 10-30%): Use sustained-release formulations.
2. Midazolam (oral bioavailability: 15-30%): Administer sublingually or intranasally.
3. Fentanyl (oral bioavailability: 20-50%): Use transdermal patches.

2. **Drugs with limited acid solubility can be challenging.[43] Here are some strategies to enhance solubility and prevent issues:**

Formulation Strategies:

1. **pH-controlled release:** Use enteric coatings or pH-sensitive polymers.
2. **Solubilizing agents:** Add surfactants, cosolvents, or solubility enhancers.
3. **Particle size reduction**: Nanoparticles, microparticles, or nanosuspensions.
4. **Solid dispersions**: Mix drugs with hydrophilic carriers.
5. **Lipid-based formulations**: Use lipids, oils, or fatty acids.

Chemical Modifications:

1. **Salt formation:** Create salts with improved solubility.
2. **Prodrugs:** Design prodrugs with enhanced solubility.
3. **Derivatization:** Modify functional groups to increase solubility.

Excipients and Additives:

1. Solubility enhancers (e.g., Tween 80, PEG 400).
2. pH modifiers (e.g., citrate, phosphate buffers).
3. Wetting agents (e.g., polysorbate 80)

Specific Examples:

1. **Ibuprofen (poor acid solubility):** Use solubilizing agents or solid dispersions. **2.**

Ketoconazole (poor aqueous solubility): Formulate with lipid-based systems.
3. Griseofulvin (poor water solubility): Use particle size reduction or solubility enhancers.

Technologies:

1. Nanotechnology
2. Microencapsulation

3. Hot melt extrusion
4. Spray drying

In Vitro and In Vivo Testing:

1. Solubility studies
2. Dissolution testing
3. Bioequivalence studies

3.For drugs that cause gastric lesions or irritation, minimizing stomach retention is crucial.[44]

Here are strategies to prevent or reduce gastric irritation and promote rapid transit: Formulation Strategies:

1. **Enteric coatings**: Delayed-release formulations that bypass stomach.
2. **pH-sensitive polymers:** Release drug in intestinal pH (e.g., Eudragit).
3. **Gastro-resistant formulations**: Use materials like cellulose acetate naphthalene
4. **Floating tablets:** Prolonged gastric retention, but reduced irritation.
5. **Mucoadhesive systems:** Adhere to intestinal mucosa, bypassing stomach.

Drug Delivery Systems:

1. Capsules or tablets with intestinal targeting.
2. Colon-specific delivery systems.
3. Delayed-release pellets or granules.

Pharmacokinetic Enhancers:

1. Gastric acid-reducing agents (e.g., omeprazole).
2. Cytoprotective agents (e.g., misoprostol).
3. Anti-ulcer medications (e.g., ranitidine).

Chemical Modifications:

1. **Prodrugs:** Design prodrugs that convert to active drug in intestines.
2. **Derivatization:** Modify functional groups to reduce gastric irritation.

Excipients and Additives:

1. Gastro-protective excipients (e.g., sucralate).
2. Anti-inflammatory agents (e.g., ibuprofen).

3. Solubility enhancers (e.g., Tween 80).

Specific Examples:

1. **Aspirin (gastric irritant):** Enteric-coated or gastro-resistant formulations.
2. **Ibuprofen (gastric irritant):** Use solubility enhancers or gastro-protective excipients.
3. **Naproxen (gastric irritant):** Delayed-release or intestinal-targeting formulations

In Vitro and In Vivo Testing:

1. Dissolution testing.
2. Gastric irritation studies (e.g., rat gastric mucosal damage).
3. Bio equivalence studies.

4. **Drugs with limited solubility can be a challenge for Gastro Retentive Floating Drug Delivery Systems (GRFDDS).**

To prevent or overcome this limitation, several strategies can be employed:

1. **Solubility enhancement:**

Use solubilizing agents, such as surfactants, cosolvents, or complexing agents, to increase drug solubility.

2. **Particle size reduction:** Reduce drug particle size to increase surface area and enhance dissolution.
3. **Crystal engineering:** Modify drug crystal form or habit to improve solubility.
4. **Salt formation:** Convert drug to a more soluble salt form.
5. **Prodrug approach:** Design a prodrug that is more soluble and converts to the active drug in vivo.
6. **Use of surfactants:** Include surfactants in the formulation to enhance drug solubilization.
7. **Co-solvent systems:** Use co-solvent systems to enhance drug solubility.
8. **Micellar systems:** Use micellar systems to solubilize drugs.
9. **Lipid-based systems:**Use lipid-based systems, such as liposomes or solid lipid nanoparticles, to enhance drug solubility
10. **Drug complexation**: Complex drug with cyclodextrins or other molecules to enhance solubility.

5. **To prevent increased formulation costs in Gastro Retentive Floating Drug Delivery Systems (GRFDDS):[45]**

1. **Optimize formulation compositi0n :** Use cost-effective excipients and active ingredients.
2. **Simple and robust manufacturing processes:** Develop simple and robust manufacturing processes to reduce production costs.

3. **Use of generic or off-patent materials:** Utilize generic or off-patent materials to reduce material costs.

4. **Economies of scale:** Scale up production to reduce costs per unit.

5. **Cost-effective drug loading methods:** Use cost-effective drug loading methods, such as spray drying or granulation.

6. **Minimize unnecessary components:** Remove unnecessary components or features that add cost without providing value.

7. **Use of biodegradable materials:** Utilize biodegradable materials that are cost-effective and environmentally friendly.

8. **Optimize packaging;** Optimize packaging to reduce material usage and costs.

9. **Supply chain optimization:** Optimize supply chain management to reduce costs associated with raw materials and logistics.

10. **Continuous process improvement**: Regularly review and improve manufacturing processes to reduce waste and costs.

6. **To prevent salivation and swallowing during drug delivery via Gastro Retentive Floating Drug Delivery Systems (GRFDDS), the following strategies can be employed:[46]**

Salivation prevention:

1. Use of salivation reducers: Co-administer salivation reducers like atropine or scopolamine.
2. Dry mouth agents: Use dry mouth agents like Anticholinergics or decongestants.
3. Mucoadhesive agents: Use mucoadhesive agents that stick to the mucosa, reducing salivation.

Swallowing prevention:

1. **Floating systems:** Design floating systems that remain in the stomach, reducing the likelihood of swallowing.
2. **Large size:** Design large systems that cannot be swallowed.
3. **Geometric configuration:** Use geometric configurations that prevent swallowing.
4. **Mucoadhesive systems:** Use mucoadhesive systems that adhere to the mucosa, preventing swallowing.
5. **Gastroretentive agents** Use gastroretentive agents like floating polymers or effervescent system
6. **Swallowing deterrents:** Use swallowing deterrents like bitter-tasting agents or unpleasant textures.
7. **Controlled release**: Use controlled release systems that release drug slowly, reducing the likelihood of swallowing.

Commonly used drugs in Gastro Retentive Floating system[47,48,49,50]

Here are some drugs that are commonly used in Gastro Retentive Drug Delivery Systems (GRDDS):

1. Antacids (e.g., Tums, Rolaids)
2. Anti-diabetic drugs (e.g., Metformin, Glipizide)
3. Anti-hypertensive drugs (e.g., Amlodipine, Lisinopril)
4. Proton pump inhibitors (e.g., Omeprazole, Lansoprazole)
5. H2 receptor antagonists (e.g., Ranitidine, Famotidine)
6. Antihistamines (e.g., Diphenhydramine, Loratadine)
7. Anti-inflammatory drugs (e.g., Ibuprofen, Naproxen)
8. Antibiotics (e.g., Clarithromycin, Amoxicillin)
9. Antifungal drugs (e.g., Fluconazole, Itraconazole)
10. Gastroprokinetic agents (e.g., Domperidone, Metoclopramide)
11. Anti-emetic drugs (e.g., Ondansetron, Granisetron)
12. Calcium supplements (e.g., Calcium carbonate, Calcium citrate)
13. Vitamin B12 supplements
14. Iron supplements (e.g., Ferrous sulfate, Ferrous gluconate)
15. Anti-osteoporosis drugs (e.g., Calcium, Vitamin D) These drugs are often formulated as:

- Floating tablets or capsules
- Gastroretentive granules or powders
- Mucoadhesive tablets or patches
- Effervescent tablets or powders
- Modified-release tablets or capsules

Marketed drugs in Gastro Retentive Floating System[51,52]

Here are some marketed drugs in gastro retentive floating drug delivery systems [1]:

- **Albuterol:** This drug is absorbed from the stomach, making it a good candidate for GRFDDS.
- **Ranitidine:** This drug is labile at alkaline pH, which can be problematic for traditional drug delivery systems.
- **Metformin:** Similar to ranitidine, metformin is also labile at alkaline pH.
- **Furosemide:** This drug is poorly soluble at alkaline pH, making GRFDDS a good option.

- **Diazepam:** Similar to furosemide, diazepam is also poorly soluble at alkaline pH.
- **Levodopa:** This drug has a narrow window of absorption, which can be challenging for traditional drug delivery systems.
- **Riboflavin:** Similar to levodopa, riboflavin also has a narrow window of absorption.

Modern technologies used in Gastro Retentive Floating System[53]

Some modern technologies used in Gastro Retentive Floating Drug Delivery Systems (GRFDDS) include:

1. **3D printing**: Creating customized floating devices with complex geometries.
2. Nanotechnology: Developing nanoparticles or nanoemulsions for enhanced drug delivery.
3. **Microencapsulation:** Encapsulating drugs in microspheres or microcapsules for controlled release.
4. **Coating technologies:** Applying specialized coatings for controlled drug release and targeting.
5. **Effervescent systems:** Using effervescent agents to create CO2 gas, enhancing floating and drug release.
6. **Swollen polymer systems:** Utilizing polymers that swell in gastric fluid, increasing retention time.
7. Floating granules: Developing granules that float and release drugs in a controlled manner.
8. **Gastroretentive polymers**: Using polymers that adhere to the gastric mucosa, extending retention time.
9. **Intelligent systems:** Integrating sensors, actuators, and microchips for controlled drug release and monitoring.
10. **Bioadhesive systems:** Developing systems that adhere to the gastric mucosa, enhancing retention and drug delivery.
11. **Stimuli-responsive systems:** Creating systems that respond to physiological stimuli (pH, temperature, enzymes) for controlled drug release.
12. **Advanced materials:** Utilizing advanced materials like hydrogels, dendrites, or lipidbased systems for enhanced drug delivery.

The GRDDS that are currently marketed,along with the technology they are used with drug category [54,55,56]

Sr No.	Product Name	Active Pharmaceutical Ingredient	Technology	Category	Manufacture
1	CafeclorLP	Cefaclor	Minextab Floating	Antibiotic	Galenix, France
2	InonAce Tablets	Simethicone	Foam based floating system	Antacid	Satopharma, Japan

3	CiproXR	Ciprofloxacin hydrochloride	Erodible matrix based system	Antibiotic	Bayer USA
4	Conviran	Ferrous sulphate	Colloidal gel forming FDDS	Iron supplement	Ranbaxy India
5	Meformin HCL LP	MeforminHCL	Minextab Floating	Antidiabetic	Galentix, France
6	CifranOD	Ciprofloxacin	Effervescent floating form	Antibiotc	Ranbaxy,India
7	GabpeninGR	Gabapentin	Polymer based swelling technology	Anticonvulsant	Depomed, USA
8	Glumetza	Merformine HCL	Polymer based swelling technology	Antidiabetic	Depomed, USA
9	Cytotec	Misoprostol	Bilayer floating capsule	Anti-ulcer	PharmaciaLimted,UK
10	Kadian	Morphine sulfate	-	Painrelief	Sumitomo pharm,Japan

11	Madopar	Levodopaand Benserzide	FloatingCR capsule	Antiparkinson's	Roche,UK
12	OflinOD	Ofloxacin	Gas-generating floating tablets	Antibiotic	
13	MetforminGR	Metformine HCL	Polymer based swelling technology	Antidiabetic	Depomed, USA
14	ProQuinXR	Ciprofloxacin	Polymer based swelling technology	Antibiotic	Depomed, USA
15	PrazopressXL	Prazosin	Effervescent and swelling-based floating system	Antihypertension	SunParma, Japan
16	Riomet OD	Metformine HCL	Effervescent floating system	Antidiabetic	Ranbaxy,India

GENERIC DRUGS OF GRDDS

1. Metformin (antidiabetic)
2. Acyclovir (antiviral)
3. Ranitidine (antacid)
4. Famotidine (antacid)
5. Omeprazole (proton pump inhibitor)
6. Lansoprazole (proton pump inhibitor)
7. Pantoprazole (proton pump inhibitor)
8. Esomeprazole (proton pump inhibitor)
9. Ciprofloxacin (antibacterial)
10. Ofloxacin (antibacterial)
11. evofloxacin (antibacterial)
12. Gatifloxacin (antibacterial)
13. Moxifloxacin (antibacterial)
14. Cephalexin (antibacterial)

15. Cefaclor (antibacterial)

These drugs can be formulated as floating tablets, capsules, or granules that remain in the stomach for an extended period, releasing the drug slowly and providing a prolonged therapeutic effect.

Please note that the suitability of a drug for gastroretentive floating drug delivery depends on various factors, including its physicochemical properties, pharmacokinetics, and pharmacodynamics. Additionally, the development of such a formulation requires careful consideration of factors like gastric residence time, drug release rate, and floating properties.

PATENT DRUGS IN GRDDS

1. Nexium (esomeprazole) - A proton pump inhibitor for GERD and ulcers
2. Prevacid (lansoprazole) - A proton pump inhibitor for GERD and ulcers
3. Prilosec (omeprazole) - A proton pump inhibitor for GERD and ulcers
4. Protonix (pantoprazole) - A proton pump inhibitor for GERD and ulcers
5. Aciphex (rabeprazole) - A proton pump inhibitor for GERD and ulcers
6. Zegerid (omeprazole and sodium bicarbonate) - A proton pump inhibitor and antacid combination
7. Kapidex (dexlansoprazole) - A proton pump inhibitor for GERD and ulcers
8. Dexilant (dexlansoprazole) - A proton pump inhibitor for GERD and ulcers
9. Vimovo (esomeprazole and naproxen) - A proton pump inhibitor and NSAID combination
10. Duexis (ibuprofen and famotidine) - An NSAID and antacid combination

These patent drugs can be formulated as gastroretentive floating drug delivery systems, such as floating tablets or capsules, to extend their release and absorption in the stomach, improving their efficacy and reducing dosing frequency.

Please note that the development of such formulations requires careful consideration of factors like gastric residence time, drug release rate, and floating properties, as well as compliance with regulatory requirements.

NEWER TECNOLOGIES IN GRDDS

Newer technologies in gastroretentive floating drug delivery systems include the development of novel dosage forms and production techniques such as hot-melt extrusion, melt pelletization, and pulsed plasma irradiation.

1. Additionally, researchers are exploring the use of mucoadhesive polymers, expandable systems, and superporous hydrogels to improve the gastric retention time and drug release properties of these systems.

2. Other advancements include the use of magnetic field-sensitive materials and raft- forming systems to control the gastric residence time and drug release. These technologies aim to enhance the therapeutic efficacy and patient compliance of gastroretentive floating drug delivery systems.

MANUFACTURING PROCESS IN NEWER TECHNOLOGIES

The manufacturing process in newer technologies for gastroretentive floating drug delivery systems involves several steps:

1. **Formulation development:** This includes selecting the drug, polymer, and other excipients, and developing a formulation that achieves the desired drug release profile and floating properties.

2. **Hot-melt extrusion:** This process involves melting the polymer and mixing it with the drug and other excipients, then extruding the mixture into a desired shape.

3. **Melt pelletization:** This process involves melting the polymer and drug mixture, then pelletizing it into small particles.

4. **Pulsed plasma irradiation:** This process involves treating the polymer surface with pulsed plasma to modify its properties and improve its floating behavior.

5. **Mucoadhesive polymer application:** This involves applying mucoadhesive polymers to the surface of the dosage form to enhance its retention in the stomach.

6. **Expandable system formation:** This involves creating expandable systems that can swell in the stomach and retain their shape.

7. **Superporous hydrogel formation:** This involves creating superporous hydrogels that can absorb gastric fluids and expand, retaining the drug in the stomach.

8. **Magnetic field-sensitive material application:** This involves incorporating magnetic fieldsensitive materials into the dosage form to control its gastric residence time and drug release.

9. **Raft-forming system formation:** This involves creating raft-forming systems that can float on gastric fluids and release the drug in a controlled manner.

10. **Quality control and testing:** This includes testing the final product for its floating properties, drug release profile, and other performance characteristics.

These manufacturing processes enable the production of gastroretentive floating drug delivery systems with improved performance and patient compliance.

FUTURE SCOPE

The future scope of gastroretentive floating drug delivery systems is promising, with potential applications in:

1. Improved drug delivery for gastrointestinal disorders
2. Enhanced bioavailability of poorly soluble drugs
3. Targeted drug delivery to specific regions of the gastrointestinal tract
4. Sustained release and controlled drug delivery

5. Reduced dosing frequency and improved patient compliance
6. Personalized medicine through tailored drug delivery systems
7. Combination therapy and multi-drug delivery
8. Novel routes of administration, such as implantable or injectable systems
9. Integration with digital health technologies for monitoring and control
10. Potential applications in pediatric and geriatric patients

Furthermore, ongoing research and advancements in materials science, nanotechnology, and biotechnology are expected to drive innovation in gastroretentive floating drug delivery systems, leading to:

1. Development of new materials and polymers with improved properties
2. Nanoparticle-based drug delivery systems
3. Bioresponsive and stimuli-sensitive systems
4. 3D printing and additive manufacturing techniques
5. Increased focus on patient-centric and personalized medicine approach

Overall, the future scope of GRDDS holds great potential for improving drug delivery and patient outcomes in various therapeutic areas.

CONCLUSION

GRDDS developed using the mechanism of mucoadhesive,swelling/size expansion &high density/low density floating provide an efficient means to prolong the GRT of dosage forms the advantages over conventional immediate release& continuous release dosage forms.

However the development of GRDDS requires through understanding of physiochemical properties of drugs the physiochemical limitations of GIT various formulations strategies.

To minimze the disadvantage strategies like enhancing solubility,minimize 1st pass metabolism,to prevent gastric irritation, overcome this limitation,to prevent the increased formulation cost in GRDDS [or]to prevent the salivation &swallowing during drug delivery shows great signifcant work on GIT& prevention.

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