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Review on: Gastroretentive Drug Delivery System

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A B S T R A C T

One new approach in this area is GRDDSs (Gastro Retentive Drug Delivery System). GRDDSs can ameliorate the controlled delivery of medicines that have an immersion window by continuously releasing the medicine for a prolonged period of time before it reaches its immersion purpose of writing this review was to probe, collect and present the recent as well as once literatures in further terse way with special focus on approaches which are presently employed in the extension of gastric hearthstone time. These includes floating system, swelling and expanding system, memoir/ mucoadhesive system, high viscosity system and other delayed gastric evacuating bias. The present review addresses compactly about the bracket, expression consideration for GRDDS, factors controlling gastric retention, graces, faults and operations of gastroretentive medicine delivery systems.

Keywords: gastroretentive drug delivery system ; floating system; swelling; expanding system; bio/mucoadhesive system; high density system

Introduction

GRDDS are an approach to protract gastric hearthstone time, there by targeting point-specific medicine release in the upper GIT for original or systemic effect. Gastro forgetful lozenge forms(GRDFs) are being used from a veritably long time to ameliorate remedy with several important medicines. GRDFs greatly improves the pharmacotherapy of stomach by releasing the medicine locally and therefore results into high attention of medicine at the gastric mucosa which can be sustained over a longer duration of time. GRDFs enable dragged and nonstop release of the medicine to the upper part of Gastro intestinal tract(GIT) and this significantly extend the duration of medicine release and ameliorate bioavailability of medicines that have narrow remedial window, by this way they protract dosing interval and increase compliance of the case. The purpose of this paper is to compactly describe the gastro forgetful medicine delivery(GRDD), factors related to GRDD, its advantages disadvantages, and emphasis is given over its significance over conventional form of medicine deliveries. Gastroretentive lozenge forms are designed to be retained in the gastric region for prolonged time and release incorporated medicine campaigners and thereby enable sustained and dragged input of the medicine to the upper part of the GIT therefore icing its optimal bioavailability. therefore, they not only protract the dosing intervals, but also increase the case compliance beyond the position of being controlled release lozenge forms. This operation is especially effective in delivery of sparingly answerable and undoable medicines.

Stomach Physiology

Success of GRDDS relies on the understanding of stomach physiology and related gastric evacuating process. Structurally the mortal stomach is composed of three anatomical regions fundus, body and antrum(pylorus), as depicted After a mess, the average volume of a stomach is about1.5 l, which varies from 250 to 500 ml during the inter-digestive phases(1). The part made of the fundus and the body acts as a force of any undigested material, while the antrum performs as the star point for the mixing action. Being the lower part, the antrum works as a pump for gastric evacuating by a propelling action. Pylorus acts to separate the stomach from the duodenum and plays a major part in gastric hearthstone time of the ingested accoutrements . still, the pattern of the gastric motility is different for the fasting and fed state(2). The gastric motility pattern is ranged in cycles of exertion as well asquiescence.The duration of each cycle is 90 – 120 min and it contains four phases(3). The motility pattern of the stomach is generally called migrating motor complex(MMC)(4).

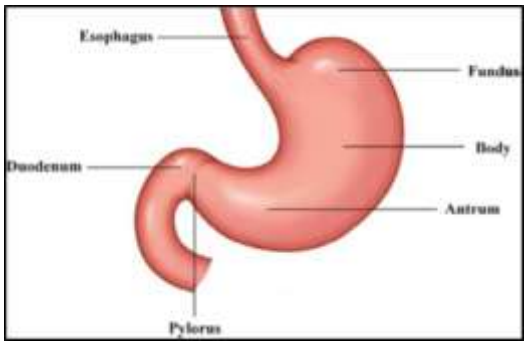

Fig. 1 – Diagram of human stomach.

Approaches to fabricate gastro-retentive systems

Different approaches have been Espoused by experimenters to enhance gastric hearthstone time with the dragged medicine release. The conception of high viscosity expression is one similar approach (Fig. 2). The developed lozenge form was made heavy(viscosity 2.5 to3.0 g/ ml) to repel in vivo peristaltic movement and remained complete in malignancy of the GIT disturbance. Consequently, the GI conveyance time was anticipated to protract for an normal of 5.8 h to 25 h(5,6). Barium sulfate, iron greasepaint, titanium oxide, and zinc oxide were incorporated in the expression to increase the viscosity of the lozenge form. Increased cure size needed to achieve that high viscosity was one of the major downsides of this kind of system, as reported by Chawla et al.(7)

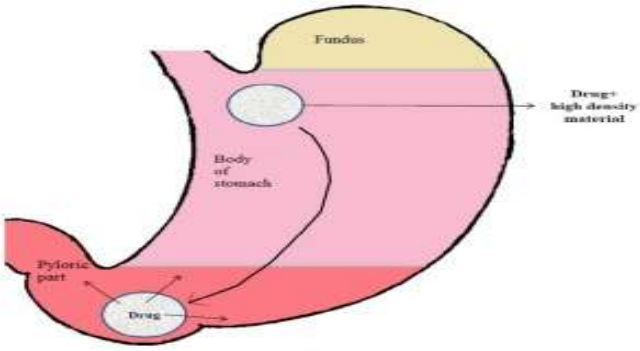

Fig. 2 – Gastro-retentive drug delivery system based on high density

Another new idea was supposed to retain the lozenge form within the stomach by the operation of a glamorous field.The lozenge form would contain magnetically active rudiments. One external attraction was needed to place on the tummy over the position of the stomach to retain the administered medicine in place(Fig. 3). Though innovative in design, lack of patient compliance was one of the major lapses for in vivo design of this delivery system(8).

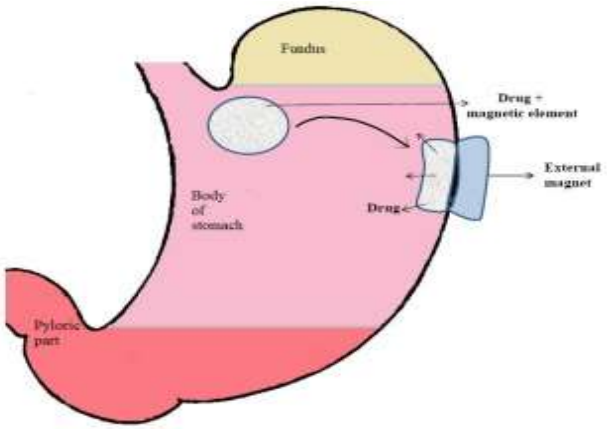

Fig. 3 – Gastro-retentive drug delivery system based on application of magnetic force.

Lozenge form to attain sustained- release specific. farther advancement With the preface of swelling and expanding system(Fig. 4), GRDDS managed to achieve significant success both in vitro and in vivo in order to retain the lozenge form in the stomach(8,9). Bolton and Desai(10) reported one similar system that was designed to increase in size bigger than the periphery of pyloric sphincter and remain logged there(Fig. 4). Alternately, the system was named as ‘ draw type systems ’ due to their pyloric sphincter blocking trait. Once the polymer came in contact with the gastric fluid, it absorbed water

and swelled(,13- 14). The selection of a suitable polymer(or combination of polymers) with an applicable molecular weight/ density grade and swelling parcels enabled the of similar kind of lozenge form has taken place with the preface of new polymers withsuper-porous nature, causing them to swell to an equilibrium size within a nanosecond. This characteristic rapid-fire lump property(swelling rate is 1100 or further) of the polymer with an average severance size of further than 100 μm occurs due to capillary wetting through several interrelated open pores when the lozenge form comes in contact with GI fluid(15).

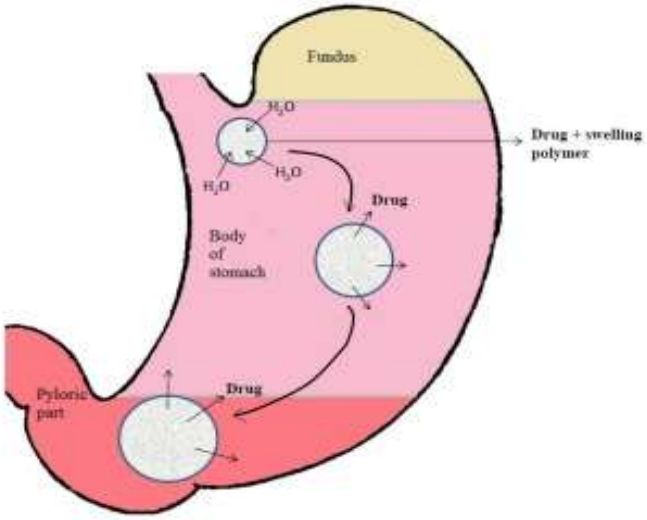

Fig. 4 – Gastro-retentive drug delivery system based on polymer swelling.

Another type of GRDDS has been designed exercising buoyancy(floating) property of any lozenge form endured in GI fluid (16). The bulk viscosity of the lozenge form attains lower than the viscosity of gastric fluid (1.004 to1.010 g/ ml) after a certainlag time. This pause time depends on the rate of lump of the polymer used in the expression, which again depends on the type, density grade, presence of wicking agent or swelling enhancers, etc.(17-19). The said parameters of the expression also determine the duration of floating as well as in vitro medicine releaserate.The efficacity of the floating geste also depends on the physiological conditions of the cases, like fed- state or fasting state, quantum of gastric fluid, etc.(20). After the needed medicine release, the used lozenge form is voided out from the stomach(21). One fresh trait similar as effervescence was incorporated within this lump- grounded floating delivery system to ameliorate the floating geste (floating pause time as well as floating duration), as shown in Fig. 5. colorful bouncy factors (e.g. sodium bicarbonate, tartaric acid and citric acid) were mixed within the lozenge form. When these factors come in contact with the gastric contents, carbon dioxide(CO2) is liberated as a result of a chemical response and it becomes trapped within the gellified hydrocolloid system. These combinations of effervescence and swelling help the lozenge form achieve effective viscosity lower than the gastric fluid and affect an upward stir onto a lozenge form which maintains the buoyancy for a prolonged period of time(22).

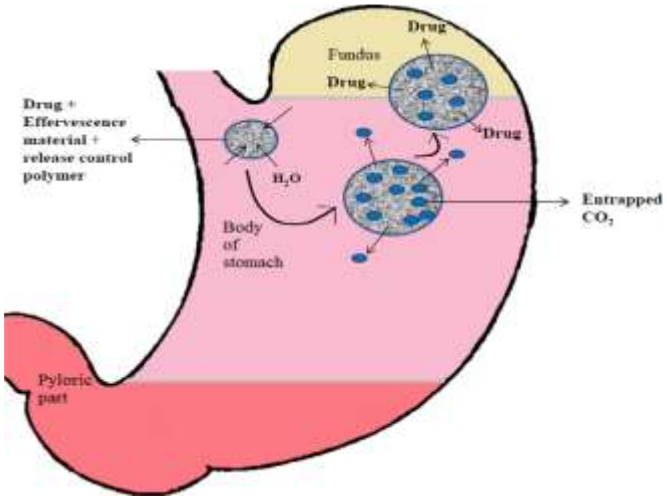

Fig. 5 – Gastro-retentive drug delivery system based on combination of polymer swelling and effervescence.

Bioadhesive or muco- tenacious medicine delivery systems were also tried as gastro-forgetful systems. The lozenge form was made to be attached inside the lumen of the stomach wall and survive the gastrointestinal motility for a longer period (Fig. 6). It was also salutary as a point specific design to promote original medicine immersion in an infected area of the stomach. Muco- tenacious excipients like polycarbophil, lectins, carbopol, chitosan, carboxymethylcellulose (CMC), pectin and gliadin were reported as expression compositions for this kind of design (23 – 25). The combination of

macho- adhesion and floating or swelling medium is being espoused as another new approach for bettered gastro- retention attributes (26,27). In- situ gelling fashion(also known as raft forming system) in combination with carbon dioxide bubble ruse was also reported as another case compliance design for gastroretention. This type of delivery system, originally as a result form, contains sodium alginate as in situ gel forming polymer along with carbonates or bicarbonates as bouncy agents. When they come in contact with the gastric fluid, they swell and induce a thick cohesive gel that contains entrapped carbon dioxide bubbles, causing the medicine delivery systems to float. For gastroesophageal influx treatment, raft forming systems are constantly used because of their tendency to produce a subcaste on the upper part of the gastric fluid(28,29).

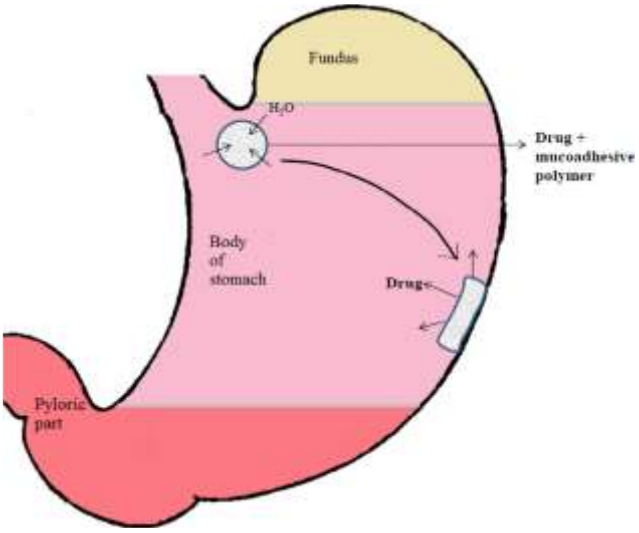

Fig. 6 – Gastro-retentive drug delivery system based on muco-adhesion.

Gastroretentive drug delivery system vs conventional drug delivery system

Sr.no		Conventional DDs	GRDDs
1	Toxin	High threat of toxin	Low threat of toxin
2	Case compliance	less	Improve patient compliance
3	Medicine with narrow immersion window in small intestine	Not suitable	Suitable
4	Medicine having rapid fire immersion through GIT	Not important profitable	Veritably important profitable
5	Medicines which degrade in colon	Not important profitable	Veritably important profitable
6	Cure jilting	High threat of cure jilting	No threat of cure jilting

Anatomy of the gastrointestinal tract

The gastrointestinal tract can be divided into three main regions videlicet

1. Stomach

2. Small intestine- Duodenum, Jejunum and Ileum .

3. Large intestine

The GIT is a nonstop muscular tube, extending from the mouth to the anus, which functions to take in nutrients and exclude waste by similar physiological processes as stashing, motility, digestion, immersion and excretion. The association of the GIT, from stomach to large intestine, is shown in Fig. 1. The stomach is a J shaped blowup of the GIT which can be divided into four anatomical regions cardia, fundus, body and antrum. The main function of the stomach is to store and mix food with gastric concealment before evacuating its cargo(chyme) through the pyloric sphincter and into the small intestine at a controlled rate suitable for digestion and immersion. When empty, the stomach occupies a volume of about 50 ml, but this may increase to as important as 1 litre when full(30). The walls of the GIT, from stomach to large intestine, have the same introductory arrangement of apkins, the different layers, from outdoors to outside, comprising serosa, longitudinal muscle, intermuscular aeroplane, indirect muscle, submucosa, muscularis mucosae, lamella propria and epithelium. In addition to longitudinal and indirect muscle, the stomach has a third muscle subcaste known as the" oblique muscle subcaste", which is positioned in the proximal stomach, raying over the fundus and advanced regions of the gastric body. The different smooth muscle layers are responsible for performing the motor functions of the GIT, i.e. gastric evacuating and intestinal conveyance(31).

Physiology of gastrointestinal tract [32]

Anatomically the stomach is divided into 3 regions:

• Fundus.

• Body.

• Antrum pylorus.

The proximal part made of fundus and body acts as a force for undigested material, whereas the antrum is the main point for mixing movements and acts as a pump for gastric evacuating by propelling conduct. Gastric evacuating occurs during fasting as well as fed countries. The pattern of motility is still distinct in the 2 countries. During the fasting state an interdigestive series of electrical events take place, which cycle through both stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle(MMC), which is further divided into following 4 phases.

Phase l: (rudimentary phase) Period of no compression

Phase ll: (preburst phase) Period of intermittent compression

Phase lll: (burst phase) Period of regular compression at the minimal frequence that resettle distally.

Phase IV: Period of transition between phase lll and phase l

After the ingestion of a mixed mess, the pattern of condensation changes from dieted to that of Fed state. This is also known as digestive motility pattern and comprises nonstop condensation as in phase 2 of dieted state. These condensation affect in reducing the size of food patches(to lower than 1 mm), which are propelled towards the pylorus in a suspense from. During the fed state onset of MMC is delayed performing in retardation of gastric evacuating rate.13 Scintigraphic studies determining gastric evacuating rate revealed that orally administered controlled released lozenge forms are subordinated to complications that of short gastric hearthstone time and changeable gastric evacuating rate

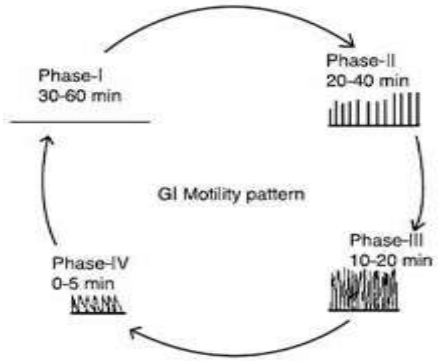

Figure.7 -A simplified schematic representation of the inter digestive motility pattern, frequency of contraction forces during each phase, and average time Period for each period.

Factors controlling gastric retention of dosage form

1. flyspeck size

Should be in the range of 1- 2 mm to pass through the pyloric faucets into the small intestine.(33)

2. viscosity

viscosity of lozenge form should be in range of 1g/ cm3 to2.5 g/ cm3

3. Size

Size should be lesser than7.5 mm in periphery.(34)

4. Shape of lozenge forms

Ring and tetrahedron bias with flexural modulus of22.5- 48 KSI(keto pound/ inch2 show 90- 100 gastric retention times(GRT).

5. Single unit/ multiple unit

Multiple units are preferable because of predictable release profile, coadministration of different units, larger safety perimeters.

6. Food input

GRT is longer in fed countries.

7. Nature, calorie content

Inedible polymers, adipose acid mariners, increase calorie content, increase acidity increases GRT, Fat and protein mess increases GRT.

8. Frequence of input

GRT increases 400 times due to low frequence of MMC

9. Posture

Varies between chine and upright itinerant countries.

10. Gender

Ladies have shorter GRT than males.(35)

11. Age

Age> 70 shows longer GRT.(36)

12. Nature of medicine

Medicines with impact on gastro intestinal conveyance time e.g. Codeine and pharmacokinetic agents e.g. metclopramide, cisapride increases GRT. 20

13. Other factors

• Diseased countries of the existent(habitual complaint, diabetes etc.)

• Body mass indicator

• Physical exertion

• Molecular weight and lipophilicity of the medicine depending on its ionization state.(37)

Drugs those are suitable for grdds[38]

1. medicines that have narrow immersion window in GIT(e.g. L- DOPA, p- aminobenzoic acid, furosemide, riboflavin)

2. medicines those are locally active in the stomach(e.g. misroprostol, antacids)

3. medicines those are unstable in the intestinal or colonic terrain(e.g. captopril, ranitidine HCl, metronidazole)

4. medicines that disturb normal colonic microbes(e.g. antibiotics used for the eradication of Helicobacter pylori, similar as tetracycline, clarithromycin, amoxicillin)

5. medicines that parade low solubility at high pH values(e.g. diazepam, chlordiazepoxide, verapamil)

Drus those are unsuitable for grdds

1. medicines that have veritably limited acid solubility e.g. Phenytoin etc.

2. medicines that suffers insecurity in the gastric terrain e.g. Erythromycin, Rabeprazole, Clarithromycin, Esomeprazole etc.

3. medicines intended for picky release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

Application of gastroretentive drug delivery system

1) Enhanced Bioavailability:- Bioavailability of riboflavin controlled release gastroretentive lozenge forms is significantly bettered compared to administration of non-controlled release gastroretentive lozenge forms polymeric phrasings. There are multitudinous different procedures, related to immersion and conveyance of medicine in the GIT, which act concomitantly to impact the magnitude of medicine immersion.(Cook JD et al., 1990)

2) Sustained medicine Delivery:- Oral controlled release phrasings are faced with problems like GRT in the gastrointestinal tract. HBS systems can be used to overcome the problems that can remain in stomach for prolonged period of time and have bulk viscosity.

3) point Specific medicine Delivery Systems:- These systems are constantly salutary for medicines which are especially absorbed from stomach or the proximal part of small intestine. The controlled/ slow delivery of medicine to the stomach offers acceptable original remedial situations and limits the systemic exposure to medicine. This decreases side goods that are produced by medicine in blood rotation. Also, the extended gastric vacuity of a point directed delivery system may reduce the frequence of dosing. E.g., Furosemide and Riboflavin.(Menon A etal., 1994))

4) immersion improvement:- medicines that are having poor bioavailability due to point specific immersion from upper part of the gastrointestinal tract are implicit campaigners to be formulated as FDDS, therefore maximizing their immersion.(Rouge N etal., 1998)

5) Minimized adverse exertion at the colon:- Retention of medicine in HBS systems at the stomach reduces the quantum of medicine that extents the colon. Hence, undesirable conditioning of medicine in the colon can be banned. This pharmacodynamics aspect offers the explanation for gastroretentive lozenge form for beta lactam antibiotics which are absorbed only from small intestine, and whose presence in colon leads to the growth of microorganism resistance.

6) Reduced oscillations of medicine attention:- Constant input of medicine following controlled release GRDF administration produces blood medicine attention within narrower range related to immediate release lozenge forms. Hence, oscillations in medicine goods are reduced and attention dependent adverse goods that are related with peak attention can be banned.

Advantages of gastroretentive drug delivery system

1. Enhanced bioavailability

The bioavailability of riboflavin CR- GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric phrasings. There are several different processes, related to immersion and conveyance of the medicine in the gastrointestinal tract, that act concomitantly to impact the magnitude of medicine immersion.(42)

2. Enhanced first- pass biotransformation

In a analogous fashion to the increased efficacity of active transporters flaunting capacity limited exertion, the pre-systemic metabolism of the tested emulsion may be vastly increased when the medicine is presented to the metabolic enzymes(cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a gel cap input.(43)

3. Sustained medicine delivery/ reduced frequence of dosing

For medicines with fairly short natural longevity, sustained and slow input from CR- GRDF may affect in a flip- bomb pharmacokinetics and enable reduced dosing frequence. This point is associated with bettered patient compliance, and thereby improves remedy.

4. Targeted remedy for original affections in the upper GIT

The dragged and sustained administration of the medicine from GRDF to the stomach may be profitable for original remedy in the stomach and small intestine. By this mode of administration, remedial medicine attention may be attained locally while systemic attention, following medicine immersion and distribution, are minimum.

5. Reduced oscillations of medicine attention

nonstop input of the medicine following CRGRDF administration produces blood medicine attention within a narrower range compared to the immediate release lozenge forms. therefore, oscillations in medicine goods are minimized and attention dependent adverse goods that are associated with peak attention can be averted. This point is of special significance for medicines with a narrow remedial indicator.(44)

6. Minimization of oscillations in medicine attention

It makes it possible to gain certain selectivity in the inspired pharmacological effect of medicines that spark different types of receptors at different attention.

7. Reduced counter-activity of the body

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

8. Extended time over critical (effective) concentration

For certain drugs that have non-concentration dependent pharmacodynamics, such as etal actam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical attention and therefore enhances the pharmacological goods and improves the clinical issues.

9. Minimized adverse exertion at the colon

Retention of the medicine in the GRDF at the stomach minimizes the quantum of medicine that reaches the colon. therefore, undesirable conditioning of the medicine in colon may be averted. This pharmacodynamic aspect provides the explanation for GRDF expression for beta- lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

10. Point specific medicine delivery

A floating lozenge form is a doable approach especially for medicines which have limited immersion spots in upper small intestine25. The controlled, slow delivery of medicine to the stomach provides sufficient original remedial situations and limits the systemic exposure to the medicine. This reduces side goods that are caused by the medicine in the blood rotation. In addition, the prolonged gastric vacuity from a point directed delivery system may also reduce the dosing frequence.

Disadvantages of gastroretentive drug delivery system

1. infelicitous for medicines with limited acid solubility. E.g. Phenytoin

2. infelicitous for medicines that are unstable in acidic environment. E.g., Erythromycin

3. medicines that irritates or causes gastric lesions on slow release. E.g. Aspirin & NSAID's

4. medicines that absorb widely in colon. E.g. Corticosteroid

5. medicines that absorb inversely well through GIT .E.g. Isosorbide dinitrate, Nifidipine

6. Floating medicine delivery systems bear high fluid position in stomach to float and work effectively.

Future potential

The control of medicine release biographies has been a major end of pharmaceutical exploration and development in the once two decades and might affect in the vacuity of new products with new remedial possibilities and substantial benefits for cases. It's anticipated that colorful new products using gastroretentive medicine delivery technologies may enhance this possibility. farther examinations may concentrate on the following generalities

• Design of an array of gastroretentive medicine delivery systems, each having narrow GRT for use according to the clinical need, e.g., lozenge and state of conditions.

•The quantitative effectiveness of gastroretentive medicine delivery systems in the dieted and fed countries.

• Determination of minimum cut- off size above that lozenge forms retained in the GIT for for dragged period of time.

• Design and development of gastroretentive medicine delivery systems as a salutary strategy for the treatment of gastric and duodenal cancers.

• Development of colorful anti-reflux expression exercising gastroretentive technologies.

• Exploring the eradication of Helicobacter pylori by using colorful antibiotics.

• Design and development of gastroretentive medicine delivery systems for medicines, which are implicit to treat Parkinson's complaint.

.Study of the effect of colorful geometric shapes in a further inordinate manner than former studies.

• Design and conflation of new polymers according to their clinical and pharmaceutical need.

• Design and conflation of new mucoadhesive agents to develop bioadhesive medicine delivery systems for bettered gastroretention.

Marketed product of grdds

• Some of the marketed formulations are listed as follows:

Brand name	**Delivery system**	**Drug dose**	**Company name**
Valrelease	Floating capsule	Diazepam	Hoffman-laroche,USA
Madopar HBS (prolopa HBS)	Floating CR capsule	Benserazide(25mg) and l-dopa (100mg)	Roche product,USA
Liquid gaviscon	Effervescent floating liquid alginate preparation	Al hydroxide(95)mg, carbonate (358)mg	Glaxosmithkline, india
Topalkan	Floating liquid alginate	Al-Mg antacid	Pierre fabre drug, France
Almagnate flot coat	Floating dosage form	Al-Mg antacid	……..
Conviron	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, india
Cycotech	Bilayer floating capsule	Misoprostol	Pharmacia , USA
Cifran OD	Gas generating floating form	Cifrofloxacin(1gm)	Ranbaxy ,india

Conclusion

Grounded on the literature check, it can be concluded that GRDDs offers colorful implicit advantages for medicines with poor bioavailability. medicine immersion in the gastro intestinal tract is a largely variable process and dragging gastric retention of the lozenge form extends the time for medicine immersion. The control of gastro intestinal conveyance of orally administered lozenge forms using GRDD systems can ameliorate the bioavailability of medicines that parade point specific immersion. GRDFs also give an fresh advantage for medicines that are absorbed primarily in the upper member of GIT, i.e., stomach, duodenum and jejunum. Different approaches for GRDD are studied each having their own advantages and disadvantages. Due to unpredictability of mortal GIT development of effective GRDFs is a real challenge to pharmaceutical technology as the medicine delivery system must remain for a sufficient time in the stomach which isn't compatible with normal physiology.

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