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Gastro-retentive drug delivery systems: a review with focus on floating drug delivery systems

Durga Srinivasarao M[1], Saravanakumar K[*2], Chandra Sekhar Kothapalli Bannoth[3]

[1]Research Scholar, Pharmaceutical Sciences, Jawaharlal Nehru Technological University Ananthapur (JNTUA), Ananthapuramu- 515002, Andhra Pradesh, India
[2]Department of Pharmaceutical Sciences, Sree Vidyanikethan College of Pharmacy, A. Rangampet, Tirupati -517502, Chittoor Dist., Andhra Pradesh, India
[3]Department of Chemistry, Krishna University, Machilipatnam-521001, Krishna Dist., Andhra Pradesh, India

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Abstract

Gastro-retentive drug delivery systems (GRDDS) attributes to gastric maintenance time combined with the medication discharge for expanded time has essentially improved patient consistency. Medications for which the chief fundamental site of ingestion is the stomach or the proximal piece of the small digestive tract or have the assimilation issue in the distal piece of the digestive system are reasonable for GRDDS. Orally sustaining or controlling the drug release combined with gastric retention property can avoid recurrent dosing in the case of drugs with short half-lives. GRDDS is also effective in locally treating gastric and duodenal ulcers, including oesophagitis and *Helicobacter pylori* infections. In this current survey, the physiology of the stomach alongside its motility design, typically called migrating motor complex (MMC), was discussed. Various approaches to GRDDS with a focus on floating drug delivery systems (FDDS) were reviewed. The vacillations in plasma drug focus are limited and portion subordinate unfriendly impacts can be forestalled by FDDS, particularly for the medications with a restricted restorative list. Slow arrival of the medication into the body by means of FDDS limits the counter movement prompting higher medication proficiency. Further, the Advantages, limitations, suitable drug candidates, factors affecting and Future challenges of FDDS were discussed.

*Corresponding Author

Name: Saravanakumar K
Phone: 9000090348
Email: kumarpharmacy156@gmail.com

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INTRODUCTION

Oral drug delivery systems (ODDS) occupied the majority among the various marketed formulations; the faster gastric emptying rate is one of the major drawbacks to the limited success of conventional dosage forms (Nayak *et al.*, 2010). Which can be overcome due to the current technological advancement; among them, the gastro-retentive drug delivery system (GRDDS) is one such example in which gastric retention time coupled with the extended drug release has significantly improved patient compliance (Ishak, 2015). By prolonging the gastric retention of drugs that are less soluble in intestinal pH, their solubility can also be improved and

the degradation of certain drugs in the colonic area can be prevented (Pawar *et al.*, 2012). The history of GRDDS was set up in recent many years, their fundamental plan and assessment boundaries were grounded. Indeed, even in the new occasions numerous surveys on GRDDS were introduced, they are significantly centred around the detailing viewpoints or in vitro portrayal examines; still, the quantity of advertised GRDDS isn't huge. The point of this audit is, to sum up, the GRDDS, with a unique spotlight on drifting medication conveyance framework (Mandal *et al.*, 2016).

Stomach physiology

Considering the physiology and exhausting cycle of the stomach are fundamental for the effective plan of GRDDS. The human stomach is made out of three locales (fundus, body and pylorus). The normal volume of a stomach is about 1.5 L after a feast; during the between stomach related stages, it differs from 250 to 500 mL. The fundus and the group of the stomach goes about as a repository, while the pylorus plays out the blending of food material. By a pushing activity, the pylorus goes about as a siphon for gastric purging; and assumes a significant part in gastric home time. The motility example of the stomach is typically called the moving engine complex (MMC); it is diverse for the fasting and taken care of state (Arnold and Hunkeler, 2015). It comprises of different cycles, the length of each cycle is 90-120 min and it contains four stages, as referenced in (Figure 1).

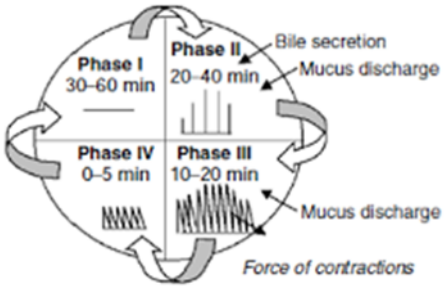

Figure 1: Different Phases of MMC Cycle

Approaches to GRDDS

Different approaches for GRDDS are,

High-Density Systems

The high-density frameworks density is going from 2.5 to 3.0 g/mL to withstand in vivo peristaltic development and stayed flawless notwithstanding the GIT unsettling influence. The density of the measurements structures is expanded with barium sulfate, iron powder, titanium oxide, and zinc oxide fuse. The significant downside of this framework is expanded portion size to accomplish high density (Mayur *et al.*, 2013), (Figure 2).

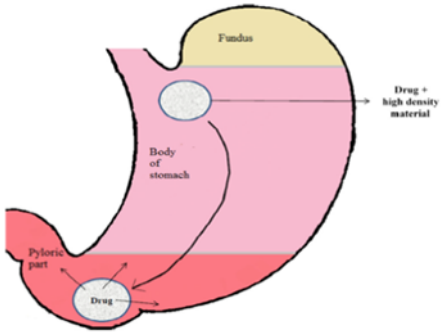

Figure 2: Gastro-retentive medication conveyance framework dependent on the high thickness

Magnetic systems

In these frameworks, by the use of the attractive outer field the structure of the measurement was held inside the stomach. The dose structure would contain attractively dynamic components (Jain and Sankar, 2013). One outer magnet was needed to position on the midsection over the area of the stomach to hold the controlled dose structure set up (Figure 3). The significant downside of this framework is the absence of patient consistence.

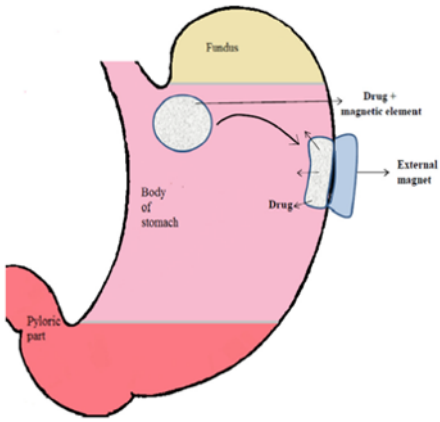

Figure 3: Gastro-retentive medication conveyance framework dependent on the utilization of attractive power

Modified shape and swelling systems

Huge achievement both in vitro and in vivo was accomplished in holding the dose structure in the stomach by growing and extending frameworks. These frameworks increment in size greater than the distance across of pyloric sphincter and remain logged there; thus, they are likewise called 'plug type frameworks' (Figure 4). When the polymer interacted with the GIF, it ingested water and expand (Narang, 2011). The determination of a reasonable polymer(s) with a suitable thick-

ness grade empowered the structure of the measurement to accomplish supported delivery qualities. Novel super-permeable polymers with fast-expanding nature (growing proportion is 1:100 or more) further prompts the headway of these frameworks.

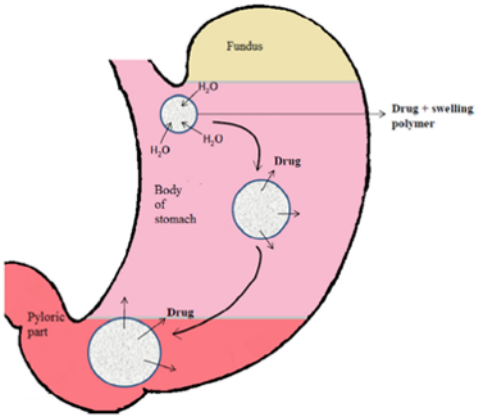

Figure 4: Gastro-retentive medication conveyance framework dependent on polymer expanding

Bioadhesive/Mucoadhesive systems

The systems will attach to the mucosal lining of the stomach wall and resist gastric emptying for a longer period (Figure 5). Hence, these are called bioadhesive or mucoadhesive systems (Jani *et al.*, 2013). It also aids in the local drug delivery. Various mucoadhesive polymers are carboxymethylcellulose (CMC), polycarbophil, chitosan, pectin, lectins, carbopol, and Gelatin.

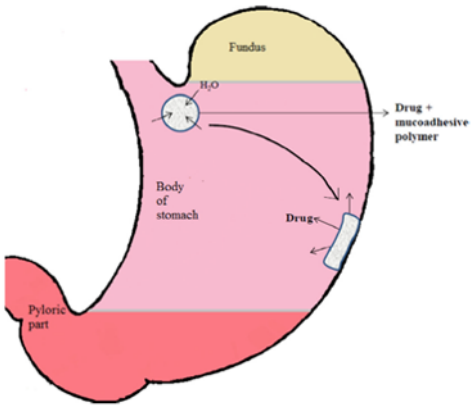

Figure 5: The gastro-retentive medication conveyance framework is dependent on mucoadhesion

Raft forming systems

These are in situ gelling system gotten by blend with carbon dioxide bubble ensnarement (Figure 6). At first, it is an answer, contains sodium alginate (in situ gel previous) alongside carbonates or bicarbonates as bubbly specialists (Li *et al.*, 2014). At the point when they interact with the GIFs, sodium alginate grows and produce a thick, strong gel that captures carbon dioxide bubbles, making it skim. They are significantly suggested for the treatment of gastroesophageal reflux.

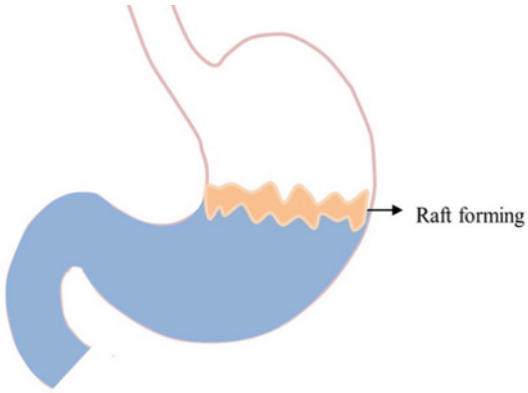

Figure 6: Raft forming systems

Floating drug delivery systems (FDDS)

FDDS is created on the idea of keeping up their density lesser than the density of the gastric liquid (1.004 to 1.010 g/mL) after a specific slack time and which permits them to glide on gastric liquids (Kaushik *et al.*, 2015). The slack time relies upon the sort and grade of the polymer utilized in the definition, which likewise decides the medication discharge rate from the detailing. Physiological components of the patients, similar to took care of or fasting state, a measure of gastric liquid, act and unhealthy state will help to the proficiency of fun. In view of the standard of lightness, FDDS can be isolated into non-bubbly and bubbly frameworks (Tiwari *et al.*, 2014).

Non-effervescent Systems

In these kinds of frameworks, measurement structures will expand immensely when interacted with gastric liquid to the degree that it keeps their exit from the stomach. By and large, these are set up by blending the medication with quickly expanding polymers, which swells when interacts with gastric liquid and keeps up their flawless shape and the mass thickness lesser than the gastric liquids; entangled air in the polymer lattice further guides the fun (Prajapati *et al.*, 2013). Different polymers utilized are hydroxypropyl methyl cellulose (HPMC), polyvinyl acetic acid derivation, Carbopol, polyethylene oxides, sodium alginate and polycarbonates. They are additionally isolated into four subtypes.

Colloidal gel hindrance frameworks

These are defined by consolidating the medication

gel-shaping hydrocolloids. They stay light on the gastric liquid, delaying the GRT, drug discharge from the measurement structure and upgrade drug ingestion at its retention site (Patil *et al.*, 2016).

Microporous compartment frameworks

In these frameworks inside a miniature permeable compartment with pores on the top and base dividers, a medication supply is exemplified. The fixed fringe dividers forestall any immediate contact of gastric liquids with the medication. The buoyancy chamber with ensnared air permits the conveyance framework to coast over the gastric liquid. Gastric liquids enter through an opening, break down the medication and convey it for ingestion (Mandal *et al.*, 2016).

Alginate globules

These are multi-unit drifting measurements structures arranged from the calcium alginate. Circular dots of roughly 2.5 mm in width can be set up by the precipitation of calcium alginate through dropping sodium alginate arrangement into the watery arrangement of calcium chloride (Lopes *et al.*, 2016). The dots are then isolated and dried; it prompts the development of a permeable framework that can keep fun for more than 5-6 h.

Hollow microspheres / Microballons

Empty microspheres/Microballons are set up by a novel emulsion dissolvable dissemination technique. Ethanol/dichloromethane arrangement of the medication and an enteric acrylic polymer was filled a fomented arrangement of polyvinyl liquor (PVA) that was thermally controlled at 40ºC. The gas stage is produced in the scattered polymer bead by the dissipation of ethanol/dichloromethane framed in the inward depression of the microsphere of the polymer and medication (Chanchal *et al.*, 2018). These micro balloons have a GRT of in excess of 12 hr.

Effervescent systems

Bubbly blend (sodium bicarbonate, tartaric corrosive and/or citrus extract) were blended inside the measurement structure; when they come to contact with the gastric liquids, carbon dioxide (CO_2) is freed because of synthetic response and it will be caught inside the lattice framework prompting its lightness because of the lesser thickness of the system (Gupta *et al.*, 2015). The bi-and tri-layered plans help in supported the arrival of one medication, which additionally have the gas-producing unit, while the other layer incorporates the second medication for guaranteed discharge. This framework can be additionally partitioned into two subtypes (Priyanka *et al.*, 2014).

Volatile Liquid Containing Systems

These frameworks contain an inflatable chamber that contains an unstable fluid (ether, cyclopentane, and so on). At internal heat level, these fluids will change over to gases and swells the chamber in the stomach and make them drift (Parsekar *et al.*, 2014). By fusing a bioerodable stop comprised of (PVA, polyethylene, and so on) gas in the inflatable chamber can be delivered after a foreordained time and these frameworks can be taken out from the stomach(Figure 7).

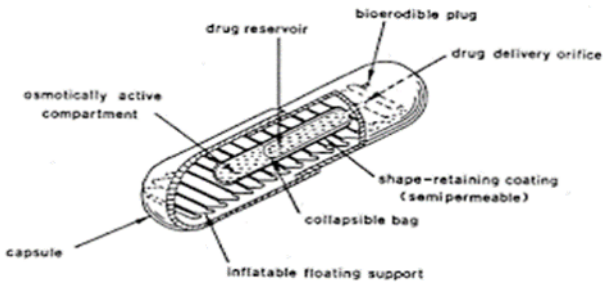

Figure 7: Volatile liquid containing system

Gas-generating systems

The bubbly responses between carbonate/bicarbonate salts and citrus/tartaric corrosive to free CO_2 happened in this conveyance framework, which gets entangled in the polymer grid of the frameworks, diminishing their thickness and make them to coast (Sarawade *et al.*, 2014). Swellable polymers like HPMC, chitosan, sodium alginate, and so forth are utilized for the development of the grid. The ideal stoichiometric proportion of citrus extract and sodium bicarbonate for gas age is accounted for to be (0.76:1). The component of gas-producing frameworks is portrayed in (Figure 8).

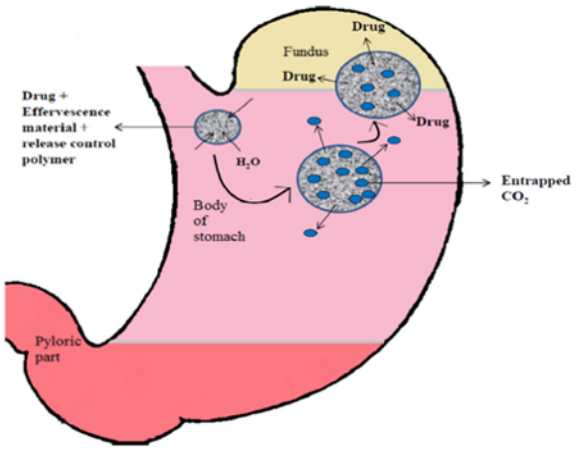

Figure 8: Gastro-retentive medication conveyance framework dependent on the mix of polymer expanding and effervescence

The blend of macho-bond and gliding or expanding

instrument is being received as another novel methodology for improved gastro-maintenance ascribes.

Merits of FDDS

The bioavailability of certain medications (for example, riboflavin and levodopa) is fundamentally improved through controlled delivery FDDS (Niharika *et al.*, 2018). By delivering the medication in a supported way through FDDS, the pre-foundational digestion of it could be extensively diminished as opposed to by a bolus contribution because of its lesser accessibility to the metabolic catalyst (CYP-3A4). By supporting the arrival of medications having a short natural half-life by means of FDDS may bring about diminishing their portion recurrence, which prompts improved patient consistence. FDDS might be helpful for nearby treatment for the aliments in the stomach may not just for the fundamental impact (Ninan *et al.*, 2018). FDDS are broadly acknowledged for drugs that have restricted retention locales in the upper small digestive tract and help in site explicit conveyance (Sopyan, 2020).

Limitations of FDDS

An elevated level of liquid in the stomach for FDDS to buoy and work effectively is required. Not appropriate for drugs that have dissolvability or soundness issue in Gastric locale, drugs (for example Nifedipine) which are all around assimilated along with the whole GIT and which goes through first pass digestion, drugs which are an aggravation to the gastric mucosa. FDDS ought to be controlled with a full glass of water (200-250 mL) which isn't attractive in the case of oblivious patients (Dave *et al.*, 2004).

Medication applicants appropriate for FDDS

Drugs that have a thin retention window in GIT (for example, L-DOPA, PABA, furosemide, riboflavin). Medications those are locally dynamic in the stomach (Shah *et al.*, 2009) (for example, misoprostol, acid neutralizers). Medications those are temperamental in the intestinal or colonic climate (Bansal *et al.*, 2003) (for example, captopril, ranitidine HCl, metronidazole). Medications that upset typical colonic organisms (for example, anti-microbials utilized for the annihilation of *Helicobacter pylori*, for example, antibiotic medication, clarithromycin, amoxicillin). Medications that show low dissolvability at high pH esteem (Talukder and Fassihi, 2004) (e.g. diazepam, chlordiazepoxide, verapamil).

Factors affecting FDDS

Density

The density of the measurement structure ought to be not exactly the gastric substance (1.004 gm/mL).

Size and Shape

Dosage structure unit with a distance across of more than 7.5 mm are accounted for to have an expanded GRT contended to those with a width of 9.9 mm. The dose structure with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kilopond per square inch (KSI) are accounted for to have better GIT for 90 to 100 % maintenance at 24 h contrasted and different shapes (Gopalakrishnan and Chenthilnathan, 2011).

Taken care of or Unfed State

Under fasting conditions, the GI motility is portrayed by times of solid engine movement or the relocating myoelectric buildings (MMC) that happens every 1.5 to 2 hours. The MMC clears undigested material from the stomach and if the circumstance of organization of the detailing harmonizes with that of the MMC, the GRT of the unit can be required to be short. Nonetheless, in the fed state, MMC is deferred and GRT is extensively more (Fell *et al.*, 2000).

Nature of the supper

Feeding of unpalatable polymers of unsaturated fat salts can change the motility example of the stomach to a took care of the state, along these lines diminishing the exhausting gastric rate and dragging out the medication discharge (Moursy *et al.*, 2003).

Caloric Content

GRT can be expanded between 4 to 10 hours with a dinner that is high in proteins (Garg and Gupta, 2008).

Applications of FDDS

FDDS offers a few applications for drugs having helpless bioavailability in view of the tight ingestion window in the upper piece of the gastrointestinal plot. It holds the structure of the measurement at the site of assimilation and, in this way upgrades the bioavailability. Different uses of FDDS are supported medication conveyance, site-explicit medication conveyance and upgraded assimilation (Zhu *et al.*, 2014).

Future challenges of FDDS

More limited FLT and bigger skimming time or gastric maintenance time (GRT) are basic for the accomplishment of FDDS, the fundamental test is to hold the conveyance framework in the stomach or the upper piece of the GIT for quite a while until all the medication have been delivered at a foreordained rate (Camilleri *et al.*, 2012).

Taken care of or abstained condition of the stomach will essentially influence the GRT, a basic boundary in the achievement of FDDS; GRT is reached out in

the fed and abbreviated in abstained states. Kind of food and its caloric worth, sex, age and stance are other physiological boundaries affecting GRT (Shah *et al.*, 2009).

High caloric worth (greasy dinners) firmly delays the cycle of the GRT. Unsaturated fat salts adjust the motility example of the stomach starved state and help in lessening gastric discharging rate (GER) (Mudie *et al.*, 2010).

The pylorus measurement (around 2 to 3 mm at stomach related stage and 12 to 13 mm at between stomach related stage) assumes a significant job in GRT of any FDDS, along these lines, particles with breadth lower than 5 mm just can pass into the duodenum through the pylorus. Size and state of the measurement structure, person's sickness state, and weight list are some different components on which GRT is reliant and identified with the viability FDDS (Mojaverian *et al.*, 1988).

Notwithstanding, it has been accounted for that occasionally, different unit FDDS shows an improved and unsurprising medication discharge contrasted with a solitary unit FDDS, as a solitary unit measurements structure may leave the stomach before it gets useful (Kong and Singh, 2009). Subsequently, to build up an ideal FDDS, the primary difficulties are to beat the issues related with the GRT of the stomach along with keeping a suitable medication discharge rate for an all-encompassing timeframe before it is processed (Lalloo *et al.*, 2012; Aoki *et al.*, 2015).

CONCLUSION

Among the different GRDDS, FDDS have gotten more fruitful and popularized. Notwithstanding, a few preferences of FDDS for patients have been seen in a greater part of cases. Portion and the assembling cycle are to be observed by case to case for medication or blends in planning FDDS. Selection of a Polymer or their combinations remains critical for the success of the FDDS. A minimum quantity that provides a maximum GRT with a significant minimum FLT and sufficient controlled release of drug from the matrix is preferred. Currently, use of matrix-forming polymer(s) together with effervescence is a highly applying technology in the design of FDDS and even various patented technologies were even been established. Regarding foundational conveyance of medications alongside improved adequacy, FDDS is required to turn out to be more famous soon. Nonetheless, because of intricacy in pharmacokinetic and pharmacodynamic boundaries, it is fundamental to build up in vivo and in vivo considers.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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