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REVIEW ON APPROCHES OF ORAL GASTRO RETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT

The purpose of this review on Oral gastro retentive drug delivery systems (OGRRDDS) was to compile the recent literature with special focus on various gastro retentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. Gastro retentive drug delivery system belongs to oral controlled drug delivery system group that are capable to retain in the stomach by passing the gastric transit. These dosage forms are also defined as floating drug delivery system, which can float in the contents of the stomach and release the drug in a controlled manner for prolonged periods of time. This review was summarized important factors controlling gastric retention. Afterwards, we have written various gastro retentive approaches designed and developed until now, i.e. Floating systems it is again divided into Effervescent and non-effervescent system (Hydro dynamically balanced system, Microporous compartmental systems, alginate beads, Hollow Microspheres), Swelling and expanding system, Bio-adhesive systems, High-density systems, Modified-shape systems, and evaluation of Gastro-Retentive Dosage Form.

KEYWORDS: OGRRDDS, Floating systems, Effervescent, non-effervescent system, Hydro dynamically balanced system, Microporous compartmental systems, alginate beads, Hollow Microspheres, Swelling and expanding system, Bio-adhesive systems, High- density systems, Modified-shape systems.

INTRODUCTION

ORAL GASTRO RETENTIVE DRUG DELIVERY SYSTEM

Gastro retentive drug delivery system belongs to oral controlled drug delivery system group

that are capable to retain in the stomach by passing the gastric transit. These dosage forms are also defined as floating drug delivery system, which can float in the contents of the stomach and release the drug in a controlled manner for prolonged periods of time.

The release rate will be controlled depending upon the type and concentration of the polymer that swells, leads to diffusion and erosion of the drug. The real challenge in the development of a gastro retentive drug delivery system is not just sustain the drug release but also to prolong the presence of the dosage form in the stomach or the upper part of the GIT until all the drug is completely released. This can be accomplished by floating drug delivery system which helps to retain dosage form in the stomach and releases the drug in controlled manner for longer period of time. GRDDS is retained for longer periods of time in the stomach e.g. hydrophilic matrix tablets, floating capsules and bio-adhesive tablet. Thus the longer period of gastric retention as compared to other oral controlled drug delivery system can be attributed. The floating results in release of the drug in to the stomach and the small intestine rather than into the large intestine where drug absorption is poor or erratic.

This is achieved by adjusting the time period of release for the drugs by changing the concentrations of polymers. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestine. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

Drugs that are required to be formulated into gastro retentive dosage forms include.

1. Drugs acting locally in the stomach .E.g. Antacids and drugs for H. Pylori viz., Misoprostol.
2. Drugs that are primarily absorbed in the stomach. E.g. Amoxicillin.
3. Drugs that is poorly soluble at alkaline pH. E.g. Furosemide, Diazepam, Verapamil, etc.
4. Drugs with a narrow window of absorption E.g. Cyclosporine, Methotrexate, Levodopa, etc.
5. Drugs rapidly absorbed from the GI tract and E.g. Metronidazole, tetracycline
6. Drugs that degrade in the colon. E.g. Ranitidine, Metformin HCl.
7. Drugs that disturb normal colonic microbe's .E.g. antibiotics against Helicobacter pylori.

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time. Dosage forms that can be retained in the stomach are called gastro-retentive drug delivery systems (GRDDS). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability.

Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the gastrointestinal (GI) tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, raft systems, expanding systems, swelling systems, bio-adhesive systems and low-density systems. Gastric retention will provide advantages such as the delivery of drugswith narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease

1.1 Factors Affecting the Gastro Retentive System

Researchers not only using old approaches but also using modified approaches to retain the dosage form in the stomach as a way of increasing the retention time. Like use of floating dosage forms , mucoadhesive systems, high-density systems, modified shape systems, gastric emptying delaying devices and coadministration of gastric-emptying delaying drugs, Raft forming system . While using these approaches GRDDS affected by various factors like.

1. **Density**

Gastric retention time is a function of dosage form buoyancy that is dependent on the density.

2. **Size**

Dosage form units with a diameter of more than 7.5 mm are.

Reported to have an increased GRT compared with those with a diameter of 9.9 mm.

3. **Shape of dosage form**

Tetrahedron and ring shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.

4. Fed or unfed state

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating my electric complexes that occurs every 1.5 to 2hours.

5. Nature of meal

Presence of food affect GRDDSs feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

6. Caloric content

If the meal contains high in proteins and fats GRT can be increased by 4 to10 hours.

7. Frequency of feed

The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

8. Gender

Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6 ±1.2 hours), regardless of the weight, height and body surface.

9. Age

Significantly longer GRT elderly people, especially those over 70.

10. Posture

GRT can vary between supine and upright ambulatory states of the patient.

11. Biological factors

Diabetes and Crohn's disease, etc.

12. Concomitant drug administration

Floating time is affected by Anticholinergics drugs like atropine and propantheline, opiates like codeine an prokinetic agents like metoclopramide And itopride.

1. 2. Requirements for Gastric Retention

Successful gastric retention is possible when the dosage form must obey following requirements.

1. Dosage form must be able to with stand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms.
2. To function as a gastric retention device, it must resist premature gastric emptying.
3. If its purpose has been served, the device should be removed from the stomach with ease.

1.3. Criteria for selection of drug for Gastro retentive drug delivery system

1. Drugs those are locally active in the stomach (e.g. misroprostol, antacids)
2. Drugs that have narrow absorption window in GIT (e.g. L-DOPA, paminobenzoic acid, furosemide, riboflavin).
3. Drugs those are locally active in the stomach (e.g. misroprostol, antacids).
4. Drugs exhibit low solubility at high pH values (e.g. diazepam, chlordiazepoxide, Verapamil).
5. Drugs that disturb normal colonic microbes such as tetracycline, clarithromycin, amoxicillin
6. Drugs those are unstable in the intestinal or colonic environment.

1.4. Drugs those are unsuitable for Gastro retentive drug delivery systems

1. Drugs that have very limited acid solubility e.g. phenytoin etc.
2. Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
3. Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

1. 5. Limitations of the Techniques of Gastro retention

1. Not suitable for drugs that that are unstable in the strong acidic environment and drugs that causes gastric lesions.
2. Bio adhesion in the acidic environment and high turnover of mucus may raise questions about the effectiveness of this technique.
3. The floating systems in patients with a Achlorhydria can be questionable in case of swellable systems, faster swelling properties are required and complete swelling of the system should be achieved well before the gastric emptying time.

1.6. Advantages of Gastro retentive drug delivery system

1. Enhanced first-pass biotransformation.
2. Sustained drug delivery/reduced frequency of dosing.
3. Targeted therapy for local ailments in the upper GIT.

4. Reduced fluctuations of drug concentration.
5. Minimization of fluctuations in drug concentration.
6. Reduced counter-activity of the body.
7. Extended time over critical (effective) concentration and Minimized adverse activity at the colon.
8. Site specific drug delivery and Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide.
9. Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance
10. E.g. beta-lactam antibiotics
11. (Penicillin's and Cephalosporin's).
12. The controlled, slow delivery of drug form gastro retentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs.
13. Gastro retentive dosage forms minimize the fluctuation of drug concentrations and effects.
14. This feature is of special importance for drug with a narrow therapeutic index.
15. Minimize the counter activity of the body leading to higher drug efficiency.
16. Reduced frequency of dosing with improved patient compliance for drugs with relatively short half life.
17. There is increase in bioavailability drugs that metabolized in the upper GIT by this Gastro retentive drug delivery approach in comparison to the administration of other drug delivery.
18. They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time as well as the gastric emptying time.
19. Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects.
20. Gastro retentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency

1. 7 Disadvantages of GRDDs

1. Unsuitable for drugs with limited acid solubility.E.g. Phenytoin
2. Unsuitable for drugs that is unstable in acidic environment. E.g. Erythromycin
3. Drugs that irritates or causes gastric lesions on slow release. E.g. Aspirin and NSAID's
4. Drugs that absorb selectively in colon. E.g. Corticosteroid

5. Drugs that absorb equally well through GIT. E.g. Isosorbide dinitrate, Nifidipine
6. Floating drug delivery systems require high fluid level in stomach to float.
7. Some drugs present in the floating system causes irritation to gastric mucosa.

1.8. Approaches to Gastric Retention

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include:

1. Floating systems.
2. Swelling and expanding system
3. Bio-adhesive systems
4. High- density systems
5. Modified-shape systems

1.8.1. Floating Drug Delivery Systems

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting 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 emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration.

FDDS can be divided into non effervescent and gas generating (effervescent) system.

1.8.1.1 Non Effervescent Systems

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. One of the formulation methods of such dosage forms involves the mixing of the 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 confers buoyancy to these dosage forms.

Ex: hydroxlypropyl methyl cellulose (HPMC), Polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

This system can be further divided into four subtypes

(i) Hydro dynamically balanced system

Contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxyl propyl cellulose, hydoxy ethyl cellulose, 5 hydroxyl propyl methyl cellulose (HPMC), polysaccharides and matrix forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the hydro colloid in the system hydrates and forms a colloid gel barrier around its surface.

(ii) Microporous Compartment System

This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption.

(iii) Alginate Beads

Multi-unit floating dosage forms have been developed from freeze-dried calcium-alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate leading to formation of a porous system,when compared with solid beads, which gave a short residence, time of 1 hr, and these floating beads gave a prolonged residence time of more than 5.5 hr.

(iv) Hollow Microspheres / Microballoons

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere

of the polymer with drug.The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 24 hr.

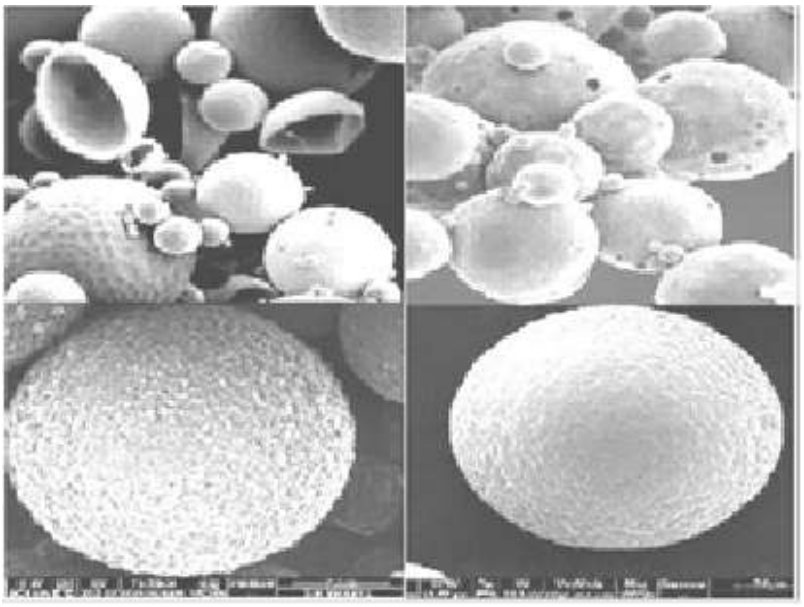

Figure: 1. Microballoons

1.8.1.2 Gas-Generating (Effervescent) Systems

These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach; carbon dioxide is released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating capsules with a core of sodium bicarbonate, lactose and poly- vinyl pyrrolidone coated with hydroxyl propyl methyl cellulose (HPMC), and floating system based on ion exchange resin system.

1.8.2. Swelling and expanding system

These are easily swallowed and reach a significantly larger size in the stomach due to swelling or unfolding processes that prolong their GRT. After drug release, their dimensions are minimized with subsequent evacuation from the stomach. Gastro retentively is enhanced by the combination of substantial dimensions with high rigidity of the dosage form to withstand the peristalsis and mechanical contractility of the stomach. Narrow absorption window drugs compounded in such systems have improved in vivo absorption properties.

1.8.3. Bio-adhesive system

Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastro retentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin, etc.

1.8.4. High-Density Systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm-3) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8-25 hours, depending more on density than on the diameter of the pellets. Commonly use excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc. These materials increase density by up to 1.5-2.4g/cm.

1.9. Evaluation of Gastro-Retentive Dosage Form

A) *In vitro* Evaluation

i) Floating systems

a) Buoyancy Lag Time

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

b) Floating Time

Test for buoyancy is usually performed in SGFSimulatedGastric Fluid maintained at 37˚C. The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

c) Specific Gravity / Density

Density can be determined by the displacement method using Benzene as displacement medium.

d) Resultant Weight

The bulk density and floating time are the main parameters for describing buoyancy. But only single determination of density is not sufficient to describe the buoyancy because density changes with change in resultant weight as a function of time. For example a matrix tablet with bicarbonate and matrixingpolymer floats initially by gas generation and entrapment but after some time, some drug is released and simultaneously some outer part of matrixing polymer may erode out leading to change in resultant weight of dosage form.

ii) Swelling systems

a) Swelling Index

After immersion of swelling dosage form into SGF at 37˚C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness diameter with time.

b) Water Uptake

It is an indirect measurement of swelling property of swellable matrix. Here dosage form is removed out at regular interval and weight changes are determined with respect to time.

Water uptake = WU = (Wt – Wo) * 100 / Wo

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

Wo = initial weight of dosage form.

B) In vitro Evaluation Test

In vitro dissolution test is generally done by using USP apparatus with paddle and GRDDs is placed normally as for other conventional tablets. But sometimes as the vessel is large and paddles are at bottom, there is much lesser paddle force acts onfloating dosage form which generally floats on surface. As floating dosage form not rotates may not give proper result and also not reproducible results. Similar problem occur with swellable dosage form, as they are hydrogel may stick to surface of vessel or paddle and gives irreproducible results. In order to prevent such problems, various types of modification in dissolution assembly made are as follows (Figure No.2).

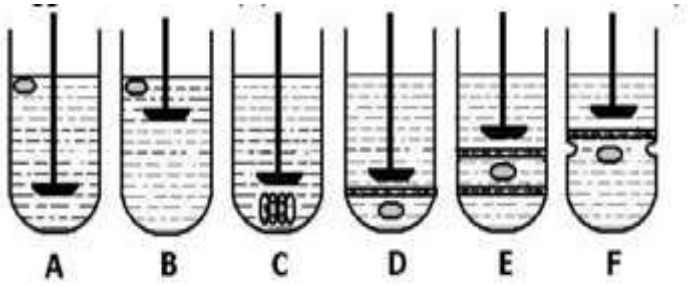

Figure No.2: Various types of modification in dissolution assembly made.

1. To prevent sticking at vessel or paddle and to improve movement of dosage form, method suggested is to keep paddle at surface and not too deep inside dissolution Medium.
2. Floating unit can be made fully submerged, by attaching some small, loose, nonreacting material, such as few turns of wire helix, around dosage form. However this method can inhibit three dimensional swelling of some dosage form and also affects drug release.
3. Other modification is to make floating unit fully submerged under ring or mesh assembly and paddle is just over ring that gives better force for movement of unit.
4. Other method suggests placing dosage form between 2 ring/meshes.
5. Change in dissolution vessel that is indented at some above place from bottom and mesh is place on indented protrusions; this gives more area for dosage form.
6. Inspite of the various modifications done to get the reproducible results. Dissolution test apparatus with modification of Rosette-Rice test Apparatus was proposed.

C) In vivo Evaluation Test

a) Radiology

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

b) Scintigraphy

To X-ray, emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is 99Tc.

c) Gastroscopy

Gastroscopy is peroral endoscopy used with fiber optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach.

d) Magnetic Marker Monitoring

In this technique, dosage form is magnetically marked with incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment. Advantage of this method is that it is radiation less and so not hazardous.

e) Ultrasonography

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

f) 13C Oceanic Acid Breath Test

13C Oceanic acid is incorporated into GRDDs. In stomach due to chemical reaction, oceanic acid liberates CO2 gas which comes out in breath. The important Carbon atom which will come in CO2 is replaced with 13C isotope. So time up to which 13CO2 gas is observed in breath can be considered as gastric retention time of dosage form. As the dosage form moves to intestine, there is no reaction and no CO2 release .

Gastro retentive products available in the market

Cifran OD ®

Brand name	**API**
Cifran OD ®	Ciprofloxacin
Madopar ®	L-DOPA and Benserazide
Valrelease ®	Diazepam
Topalkan ®	Aluminum -magnesium antacid
Almagate FlatCoa	Aluminum -magnesium antacid

CONCLUSION

Based on the literature surveyed, it may be concluded that gastroretentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. Due to complexity of pharmacokinetics and pharmacodynamics parameters, in vivo studies are required to establish the optional dosage form for a specific drug. Another promising area of research for gastroretentive drug delivery system is eradication of Helicobacter pylori, which is now believed to be causative bacterium of chronic Vol.3 Issue 1, January-March 2010 ISSN 0974-2441 Asian Journal of Pharmaceutical and Clinical Research Page 9 gastritis and peptic ulcers. Although, this micro organism is highly sensitive to many antibiotics, its complete eradication requires high concentration of antibiotics be maintained within gastric mucosa for prolonged time period. An important feature to take into account is the stomach

physiology. The time when the drug is taken (during or apart from the meal) is an important parameter. To develop an efficient gastroretentive dosage form is a real challenge to pharmaceutical technology. Indeed, the drug delivery system must remain for a sufficient time in the stomach, which is not compatible with its normal physiology. All these gastroretentive drug delivery systems (high density, floating, expandable or unfoldable or swelling, superporous, bioadhesive, magnetic systems etc.) are interesting and present their own advantages and disadvantages. Now, a lot of work is running to develop different types of gastroretentive delivery systems of various drugs. In the future, it is expected that they will become of increasing importance, ultimately leading to improved efficiencies of various types of pharmacotherapies.

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