International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 870-877 www.ijprajournal.com ISSN: 2456-4494

A Review on Gastrorete Drug Dilevery System

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Submitted: 15-05-2022 Revised: 25-05-2022 Accepted: 28-05-2022

ABSTRACT: Oral controlled release and site specific drug delivery system has been of great interest in pharmaceutical field to achieve improved therapeutic advantage. Concept of novel drug delivery system arose to overcome certain aspect related to physicochemical properties of drug molecule and the related formulations. Gastro retentive drug delivery system is one of such novel approaches to prolong gastric residence time, thereby targeting site specific drug release in the stomach for local or systemic effects. This approach is useful particularly for the drugs which have narrow absorption window in the upper part of gastro intestinal tract. In this review we have been discussed various approaches of gastro retentive drug delivery system, such as floating and non-floating systems.

KEYWORDS: floating system, non-floating system, gastric residence time, evaluation parameter.

I. INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systematiccirculation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT) [(1)] . These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose [(2).] To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment [(3).] Also prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer, etc. Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach , low density (floating) systems that causes buoyancy in gastric fluid [(4,5,6)] mucoadhesive systems that causes bioadhesion to stomach mucosa [(7)] ,unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach ,superporous hydrogel systems , magnetic systems etc. The current review deals with various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery systems

II. REVIEW OF LITERATURE:

Rabina Aslam et.al:- Gastroretentive drug delivery systems provide drug delivery at the controlled rate and prolong the retention of dosage forms in gastrointestinal tract.

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Amrjeet Daniya-et.al :- Gastric retentive dosage forms have been developed to provide controlled release therapy for drugs with reduced absorption in the lower gastrointestinal (GI) tract or for local treatment of diseases of the upper GI tract.

Vivek K Pawar et.al.:- Gastroretentive dosage forms (GRDF) receive great attention because they can improve the performance of controlled release systems. An optimum GRDF system can be defined as a system which retains in the stomach for a sufficient time interval against all the physiological barriers, releases active moi-ety in a controlled manner, and finally is easily metabolized in the body

PHYSIOLOGY OF STOMACH: Anatomically the stomach is divided into three regions Fundus, Body and Antrum (pylorus) The proximal part made of fundus and body acts as a reservoir for undigested materials, whereas the antrum is the main site for mixing motions and acts as a pump for gastric emptying by propelling actions Gastric emptying occurs in both the fasting and fed states. During the fasting state an interdigestive series of electrical events take place which cycle both through stomach and intestine every 2-3 hrs, which is called as inter digestive myloelectric cycle or migrating myoelectric cycle (MMC) which is further divided in to four phases.[8] After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state which is also termed as digestive motility pattern .

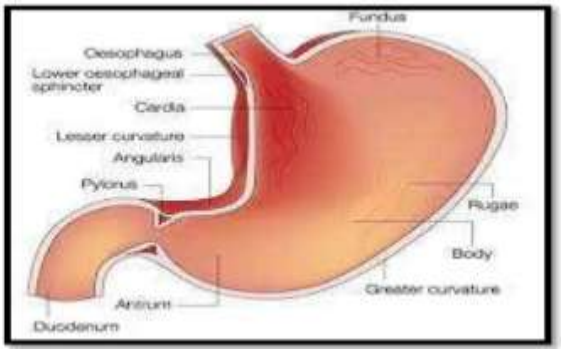

Fig.1 Structure of stomach871

Phase 1- (Basic phase) last from 30-60 minutes with rare contractions 2. Phase 2- (Preburst phase) last for 20-40 minutes with intermittent action potential and contractions. 3. Phase 3- (Burst phase) last for 10-20 minutes which includes intense and regular contractions for short period. 4. Phase 4-last for 0-5 minutes and occurs between phase 2 and 1 of 2 consecutive cycles.

Differenece

Gastroretentive drug delivery systems vs. conventional drug delivery systems

Sr.NO		Conventional DDs	GRDDs
1	Toxicity	High risk of toxicity	Low risk of toxicity
2	Patient compliance	Less	Improves patient compliance
3	Drug with narrow absorption window in small intestine	Not suitable	Suitable
4	Drug acting locally in stomach	Not much advantageous	Very much advantageous
5	Drug having rapid absorption through GIT	Not much advantageous	Very much advantageous
6	Drug which degrades in the colon	Not much advantageous	Very much advantageous
7	Dose dumping	High risk of dose dumping	No risk of dose dumping

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Merits

Delivery of drugs with fine absorption window in the small intestine region.

• Longer residence time in the stomach could be advantageous for local action in the upper portion of the small intestine, for example, treatment of peptic ulcer disease.

• Better bio-availability is expected for drugs that are absorbed readily upon release in the GI tract such as cyclosporine, ciprofloxacin, amoxycillin, captopril, etc.

• Patient compliance by making once-a-day therapy.

• Therapeutic efficacy improved.

• Moderates frequency of dosing.

• Directed therapy for local ailments in the upper GI tract.

• Prolongs the residence period of the dosage form at the site of absorption.

• Avoids the first pass metabolism.

• Outstanding accessibility.

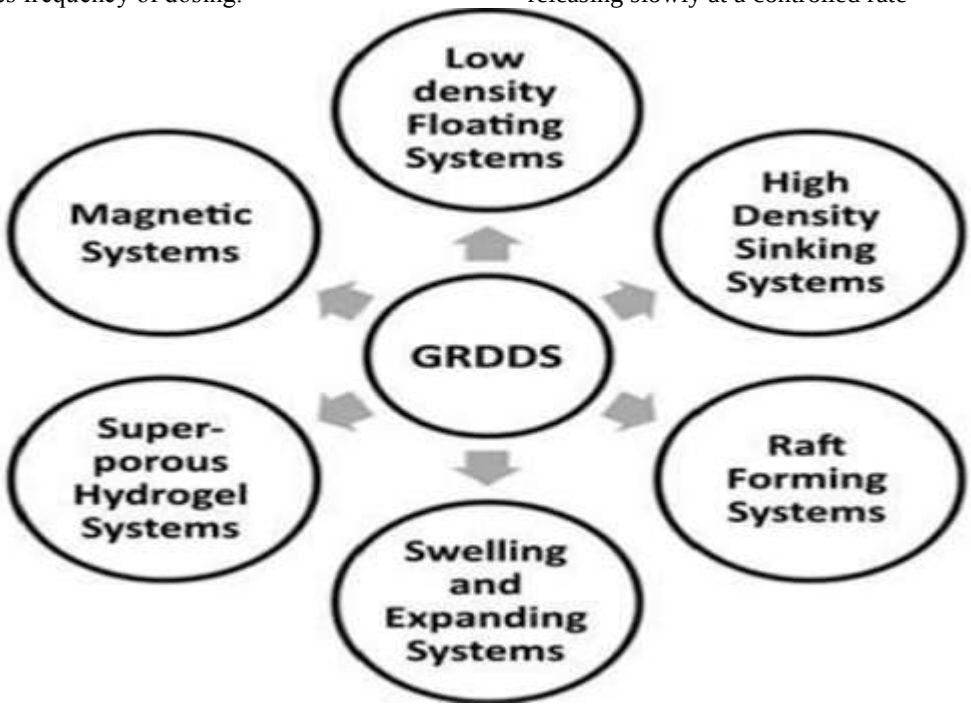
• Fast absorption because of enormous blood supply and good blood flow rates.

• Drug bioavailability increases due to first pass metabolism.

• Specific site for drug delivery.

• Decreasing mucosal irritation by drugs, by drug releasing slowly at a controlled rate.

• Reducing mucosal irritation by drugs, by drug releasing slowly at a controlled rate[9]



Types Of The Gastroretentive Dosage Form

Demerits

Floating systems have the limitation that they need high level of fluids in the stomach for floating and working efficiently. So more water drinking is prescribed with such dosage forms.

• In supine posture (like sleeping), floating dosage form may get cleared away (if not of larger size) by contractile waves. So patient must not take floating dosage form just before going to bed.

• Drugs having stability problem in high-acidic environment, having very small solubility in acidic environment, and drugs causing irritation to gastric mucosa cannot be incorporated into GRDDs.

• Swellable dosage form must be clever to swell fast before its exit from stomach and achieve size larger than pylorus aperture. It need be capable to resist the housekeeper waves of Phase III of MMC.

• Gastric retention is influenced by several factors such as gastric motility, pH and presence of food. These factors are never endless and hence the buoyancy cannot be predicted.

• The major trial for a bioadhesive system is the high turnover rate of gastric mucus.

• There is also probability of esophageal binding with bioadhesive drug delivery systems.

• Drugs which have stability and solubility problems in GIT are not appropriate candidates for these types of systems.

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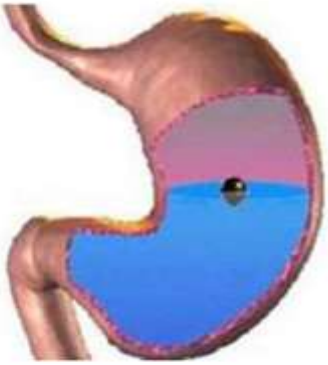
High density system:•

This approach involves formulation of dosage forms with density that must exceed density of normal stomach content (1.004g/ml). These formulations are prepared by coating drug on a heavy core or mixed with heavy inert material such as iron powder, zinc oxide, titanium dioxide, barium sulphate. The resultant pellets can be coated with diffusion controlled Membrane These systems have some drawbacks like they are technically difficult to manufacture with a large amount of drug because the dry material of which it is made interacts within the gastric fluid to release its drug contents. One other problem is that no such system is available in the market

High-density system
(density > 1 g.cm^{-3})

Floating or Low density system:

By virtue of their low densities, FDDS remain afloat above the gastric contents for prolonged periods of time and provide continuous release of the drug. These systems in particular have been extensively studied because they do not adversely affect the motility of the GIT[10] .Their dominance over the other types of GRRDS is also 19 evident from the large number of floating dosage forms being commercialized and marketed world-wide



Floating drug delivery system

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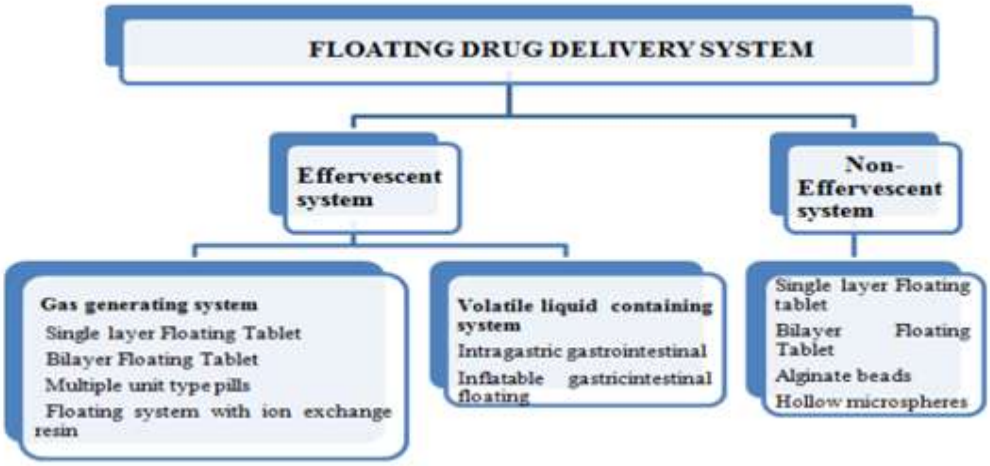
Classification of floating drug delivery System



A)Swelling system:

These are the dosage forms, which after swallowing swells to such an extent that their exit from the pylorusis prevented, as a result the dosage form is retained in the stomach for a prolonged period of time. These systems are called as plug – type system as they have the tendency to remain lodged at the pyloric sphincter. Controlled and sustained release may be achieved by selection of proper molecular weight polymer, and swelling of the polymers retard the release [11,12] ·On coming in contact with gastric fluid the polymer imbibes water and swells. The extensive swelling of these polymers is due to the presence of physical chemical cross links in the hydrophilic polymer network. These cross link prevents the dissolution of the polymer and hence maintain the physical integrity of the dosage form. In the dissolution media the membrane detached from the core and sweeled to forma balloon that kept the unit floating. the size of the units increased by three to six folds, thus the floating ability as well as the increased dimension offered the system gastroretentive property

B)Mucoadhesive System:

Mucoadhesive drug delivery systems contain a mucoadhesive polymer that adheres to the gastric mucosal surface and prolong its gastric retention in the git. The capability to adhere to the mucus gel layer makes mucoadhesive polymers very useful exicipients in the GRRDS. These polymers can be natural such as sodium alginate, gelatin, guar gum etc semisynthetic polymers such as HPMC, carbopol, sodium carboxymethyl cellulose the adhesion of polymers with mucous membrane may be mediated by hydration, bonding, or receptor mediated. In hydration mediated adhesion, the hydrophilic polymer become sticky and mucoadhesive upon hydration[11]. Bonding mediated involves mechanical or 21 chemical bonding. Chemical bonds may involve ionic or covalent bonds or vander Waal forces between the polymer molecule and the mucous membrane. Receptor mediated adhesion takes place between certain polymers and specific receptors expressed on gastric cells. The polymers can be cationic or anionic or neutral

C)Super porous hydrogel systems:

These swellable systems differ sufficiently from the conventional types to warrant separate classification. In this approach to improve gastric retention time (GRT) super porous hydrogels of average pore size >100 micro miter, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores . They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material

D)Magnetic Systems:•

This approach to enhance the gastric retention time (GRT) is based on the simple principle that the dosage form contains a small internal magnet [13] ,and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to wok, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

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Factors affecting gastric retention time of the dosage form:

a)Density- the density of the dosage form should be less than that of the gastric contents (1.004g/ml)

b)Size- dosage form having diameter of more than 7.5mm have more gastric residence time than that of 9.9mm diameter dosage form.

c)Shape of the dosage form- the tetra hedron resided in the stomach for longer period than other devices of similar size. Single or multiple unit formulationmultiple unit formulation show a more predictable release profile and insignificant impairing of the performance due to failure of the units. , allow coadministration of units with different release profile or containing incompatible

f)Caloric content - GRT can be increased by 4-10

g)Frequency of feed- The GRT can be increase over 400 min when successive meals given are compared with the single meal due to low frequency of MMC.

h)Gender- mean ambulatory GRT in male (3.4hrs) is less compared with the age and race matched female counterparts (4.6hrs) regardless of height, substances and permit larger margin of safety against dosage form failure compared with single unit dosage form.

d)Fed or unfed state- under fasting conditions, the gi motility is characterized by periods of strong motar activity that occurs every 1.5-2 hrs. The MMC sweeps undigested material from the stomach and if the timing of the formulation coincides with that of MMC, the GRT of the unit can be very short, however in fast state MMC is delayed and GRT is longer.

e)Nature of meal- feeding of indigestible polymers or fatty acids can change the motility pattern of the stomach to a fed state,thus decreasing gastric emptying rate and prolonging drug release.
with a meal that is high in protein and 15 fat.
weight and body surface.

i)Age- people with age more than 70 have a significant longer GRT

j)Concomitant drug administration- anticholinergic like atropine and propetheline opiates like codeine can prolong GRT

Commonly used drug in formulation of gastro retentive dosage forms:

Dosage form	Drug
Floating Tablets	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem
Floating Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol
Floating Microspheres	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast
Floating Granules	Diclofenac sodium, Indomethacin,
Powders	Several basic drugs

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Gastroretentive products available in the market:

Brand Name	Active Ingredient(s)
Cifran OD	Ciprofloxacin
Madopar	Benserazide and L-dopa
Valrelease	Diazepam
Topalkan	Aluminum-magnesium antacid
Cytotec	Misoprostal

III. CONCLUSION:

Lifestyle changes, including diet, exercise, and stress management,may contribute significantly to lowering of blood pressure. Supplements such as potassium, magnesium, CoQ10, omega- 3 fatty acids, amino acids Aarginine and taurine, and vitamins C and E have been effectively used in the treatment of cardiovascular disease, includinghypertension. They have proveneffective in lowering blood pressure and improving heart functions. Among themost researched and frequently utilized for hypertension are Hawthorne, Arjuna, Olive leaf, European mistletoe, Yarrow, Black cumin seeds, Forskolin, Indian snakeroot, and Garlic. More research is indicated to determine the full potential that alternative medicine has to offer in the management of hypertension. With the increasing numbers of patients sufferingfrom hypertension and conventional medicine failing to effectively control the problem, alternative therapies offer hope.

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