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Review on Gastroretentive Drug Delivery System

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ABSTRACT

Among the different routes of drug administration the oral route is most successful and popular. Dosage forms with a prolonged gastric residence and controlled drug delivery are called as Gastroretentive Drug Delivery System. Thus, these dosage forms significantly extend the period of time over which the drugs may be released in comparison to other Controlled Release Drug Delivery System. Different objectives that are to be achieved during development of gastro retentive drug delivery system are as it should increase bioavailability of drug, increase residence time of dosage form in stomach, achieve greater patient compliance by reducing frequency of dosing, better safety profile, achieve the improved economy of dosage form.

This review covers major aspects of stomach anatomy and physiology, factors, rational, objectives, approaches, evaluation of gastroretentive drug delivery system.

Keywords: Gastroretentive, Bioavailability, Stomach, Residence time.

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INTRODUCTION

Among the different routes of drug administration the oral route is most successful and popular. This may be due to the ease of administration and the fact gastrointestinal (GI) physiology offers more flexibility in dosage form than most of the other routes. Conventional oral drug delivery systems such as tablets and capsules guarantee a prompt release of the drug; but they fail to maintain the drug concentration within the therapeutically effective range for a required period. To maintain effective plasma drug concentration, these dosage forms must be administered frequently. Presently, oral controlled drug delivery systems have emerged largely to overcome the problems experienced with the conventional dosage forms. Basically, oral controlled drug delivery systems consist of a drug reservoir from which the drug is released slowly during its transits in GIT, in a predetermined rate to maintain constant absorption of the drug[1]. But in case of the oral solid drug delivery systems, despite of excellent *in-vitro* release patterns, drug absorption can be unsatisfactory and highly variable between individuals. This is due to the physiological variability such as GI transit in addition to the gastric retention time (GRT), as the GRT plays an important role in overall transit of the dosage form. Oral controlled release system can achieve slower release, but the drug released after passing the absorption site cannot be fully utilized because the GRT of the delivery system is less than 12 hrs. Hence it is not possible to deliver the drug more than 12 hrs with oral route. This has promoted researchers to retain the drug delivery system in the stomach for prolonged and predictable time. Such a prolonged gastric retention not only controls the time but also the space in the stomach by maintaining the delivery system positioned at a steady site and thereby properly delivering the drug[2].

Gastroretentive Drug Delivery System

Dosage forms with a prolonged gastric residence and controlled drug delivery are called as Gastroretentive Drug Delivery System. Thus, these dosage forms significantly extend the period of time over which the drugs may be released in comparison to other Controlled Release Drug Delivery System[3].

Suitable Drug candidate for Gastro Retentive Drug Delivery System[4]

1) Drugs acting locally in the stomach; misoprostol, 5-fluorouracil, antacids and antireflux preparations, anti Helicobacter pylori agents, and certain enzymes.

2) Drugs that are primarily absorbed in the stomach.

3) Drugs that are poorly soluble at an alkaline pH; (Drugs insoluble in intestinal fluids /(acid soluble basic drugs)) :- chlordiazepoxide, chlorpheniramine, cinnarizine, diazepam, diltiazem, metoprolol, propranolol, quinidine, salbutamol, and verapamil.

4) Drugs absorbed rapidly from GI tract.

5) Drugs that degrades in colon and unstable in lower part of GI tract: captopril.

6) Drugs exhibiting site-specific absorption in the stomach or upper parts of the small intestine: atenolol, furosemide, levodopa, p-aminobenzoic acid, piretanide, riboflavin-50-phosphate, salbutamol (albuterol), sotalol, sulpiride, and thiamine.

7) Drugs with variable bioavailability: sotalol hydrochloride and levodopa.

The drug that are not suitable for gastric retention are[5]

Drugs that have very limited acid solubility.

Drugs that suffer instability in the gastric environment.

Drugs intended for selective release in the colon.

Objectives[4]

The different objectives that are to be achieved during development of gastro retentive drug delivery system are as follows -

1) To increase bioavailability of drug.

2) To increase residence time of dosage form in stomach.

3) To achieve greater patient compliance by reducing frequency of dosing.

4) To obtained better safety profile.

5) To achieve the improved economy of dosage form.

Rationale for the use of GRDDS[4]

1) The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this Gastroretentive drug delivery approach in comparison to the administration of non-gastroretentive drug delivery. There are several different factors related to absorption and transit of the drug in the gastrointestinal tract (GIT) that act concomitantly to influence the magnitude of drug absorption.

2) For drugs with relatively short half life, sustained release may result in a flip- flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.

3) They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids.

4) Gastroretentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.

5) The controlled, slow delivery of drug from gastroretentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects.

6) Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index. 7) Gastroretentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.

8) Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.

9) The sustained mode of drug release from Gastroretentive dosage form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.

In simple ways it can be shown as in figure 1.

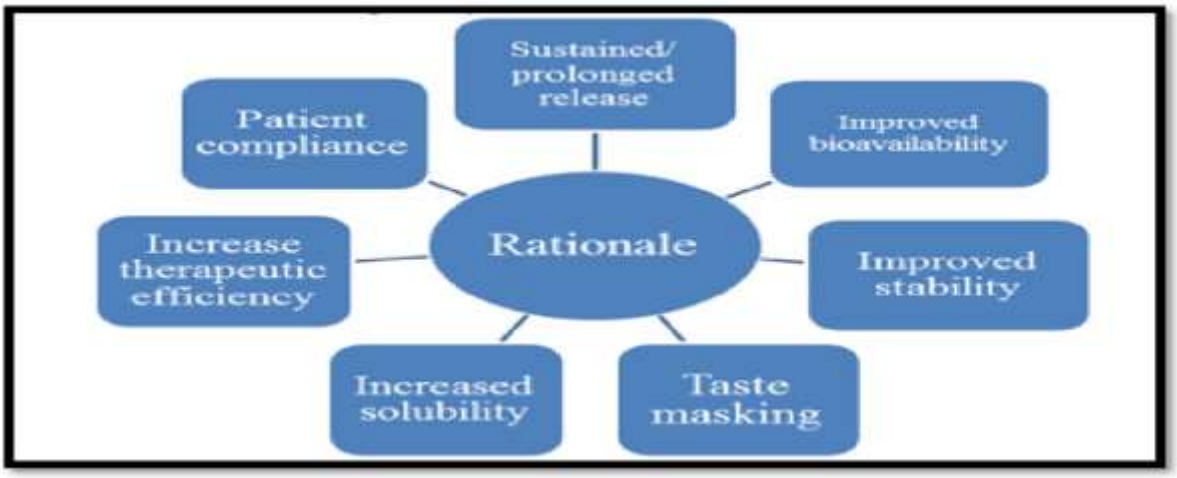

Figure 1: Rationale for the use of GRDDS

Anatomy of the stomach GIT[5]

The gastrointestinal tract can be divided into three main regions. They are namely

1. Stomach
2. Small intestine—duodenum, jejunum and ileum
3. Large intestine

The GIT (gastrointestinal tract) is a continuous muscular tube, extending from the mouth to the anus. The GIT is like a tube of 9 m long that starts from the mouth and ends with the anus (Figure 2). The function is to take in nutrients and eliminate waste by such physiological processes such as secretion, motility, digestion, absorption and excretion. The walls of the GIT, from the stomach to the large intestine, have different layers of tissue from outside to inside. The stomach has a third muscle layer known as the "oblique muscle layer" which is situated in the proximal stomach, branching over the fundus and higher regions of the gastric body. The different smooth muscle layers are responsible for performing the motor functions of the GIT, i.e. gastric emptying and intestinal transit. The stomach is a J-shaped organ. It is located in the upper left hand portion of the abdomen, just below the diaphragm. It occupies a portion of the epigastria and left hypochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Since the drugs are absorbed in the upper small intestine, it will be beneficial to develop the dosage forms that reside in that region.

The stomach is divided into 3 anatomical regions:

1. Fundus
2. Body
3. Pylorus (Antrum)

The proximal part is made of fundus, body acts as a reservoir for undigested material and antrum acts as a pump for gastric emptying by propelling actions. Antrum is a major site of mixing. Due to its small surface area very little absorption takes place from the stomach. It provides barrier to the delivery of drugs to the small intestine (Figure 3).

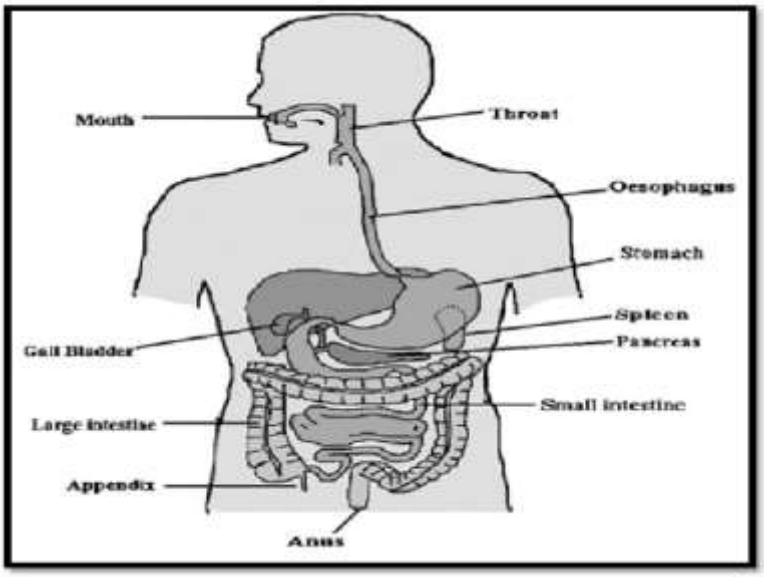

Figure 2: Anatomy of the gastrointestinal tract

Physiology of the stomach

The stomach is an expanded section of the digestive tube between the oesophagus and small intestine. In the empty state the stomach is contracted and its mucosa and sub mucosa are thrown up into folds called rugae. There are 4 major types of secretory epithelial cells that covers the stomach and extends into gastric pits and glands.

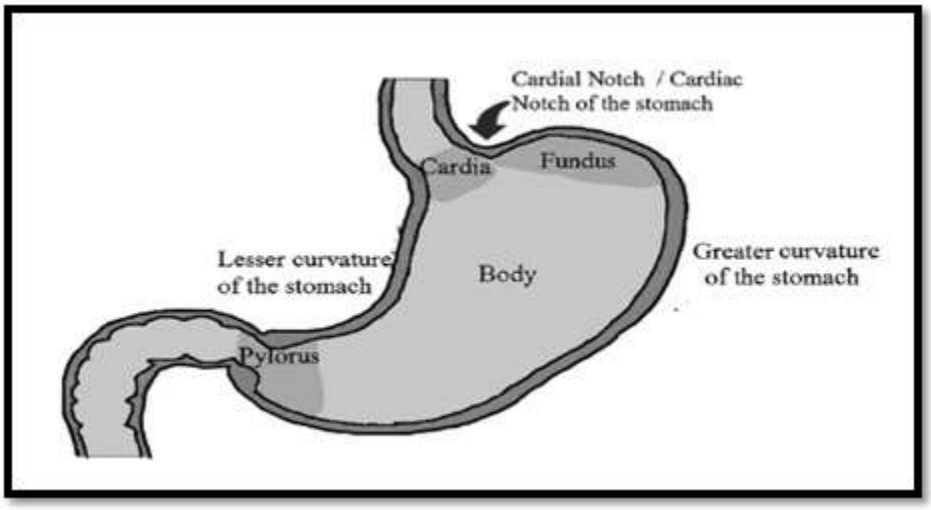

Figure 3: Physiology of the stomach

1. Mucous cells- secrete alkaline mucus
2. Parietal cells – secrete HCL
3. Chief cells- secrete pepsin
4. G cells- secrete hormone gastrin[6]

The GIT is always in a state of continuous motility. There are two modes of motility pattern such as -

(a) The digestive mode and

(b) Inter digestive mode.

Gastric emptying occurs during fasting as well as fed states. In case of fasted state an inter digestive series of electrical events occurs in cyclic manner both through the stomach and the small intestine every 2–3 h. This electrical activity is termed as inter digestive myoelectric cycle or migrating myoelectric complex (MMC).

The migrating myoelectric complex (MMC) is further divided into four phases (Figure 4):

PHASE I: It is quiescent period with rare contraction and lasting from 30 to 60 min.

PHASE II: It consists of intermittent action potentials and contraction that gradually increases intensity and frequency as the phase progresses. It lasts for 20–40 min.

PHASE III: It is for short period of intense, large regular contraction from 10 to 20 min, and it sweeps the undigested material from the stomach to the small intestine. Phase III is termed as 'housekeeper wave' as it enables to sweep away all undigested materials out of the stomach and down to the small intestine. Between phase III and phase I of two consecutive cycles a brief transitional phase IV occurs.

PHASE IV: Short transitional phase of about 0 to 5 min.

In fed state gastric emptying is slow. The motor activity in the fed state is induced 5–10 min after ingestion of a meal and persists as long as food remains in the stomach. The larger the amount of food ingested, the longer the period of fed activity, with usual time spans of 2–6 h. When GRDDS are administered in the fasted state, the MMC may be in any of its phases, which can significantly influence the total gastric retention time (GRT) and transit time in the gastrointestinal tract[5].

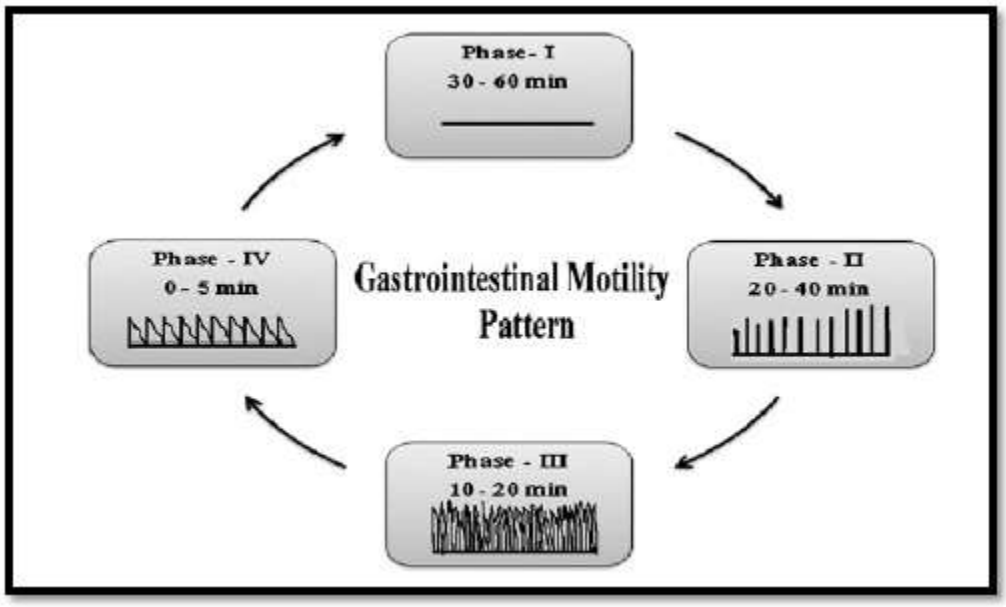

Figure 4: Schematic representation of the inter digestive motility pattern, frequency of contraction forces during each phase and average time period of each period

Factors controlling the gastroretentive drug delivery system[5]

Factors related to the dosage forms

1. Size of the dosage form

To allow the dosage form to pass through the pyloric valve into the small intestine the particle size should be in the range of 1 to 2 mm. In most cases, the larger the dosage form the greater will be the GRT. Due to the larger size of the dosage form, it could not quickly pass through the pyloric antrum into the intestine. Small-size tablets leave the stomach during the digestive phase while the large-sized tablets are emptied during the housekeeping waves.

2. Shape of dosage form

Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared to other shapes.

3. Density of dosage form

Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to the bottom of the stomach. Both positions may isolate the dosage system from the pylorus. A density of 1.0 g/cm3 is required to exhibit floating property. However the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium.

Food intake and its nature

1. Fed and unfed state—under fasting condition

Under fasting conditions, the gastrointestinal motility is characterized by periods of strong motor activity or MMC that occurs every 1.5 to 2 h. The MMC sweeps the undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

2. Food intake and nature of food

Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract influences the gastric retention time of the dosage form. Usually the presence of food in the gastrointestinal tract improves the gastric retention time of the dosage form and thus, the absorption of drugs increases by allowing its stay at the absorption site for a longer period.

3. Calorie content

The rate of gastric emptying primarily depends on the caloric contents of the ingested meal. It does not differ for proteins, fats, carbohydrates as long as their caloric content is the same. Generally an increase in acidity, osmolality, and caloric value slows down gastric emptying. GRT can be increased between 4 and 10 h with a meal that is high in proteins a

4. Frequency of feed

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

Patient related factors

1. Gender

Gastric emptying rate may differ in male and female. Generally the gastric emptying in women was slower than in men.

2. Age

Elderly people, especially those over 70 years have a longer gastroretentive time. Thus gastric emptying time is slowed down.

3. Posture

The effect of posture on GRT, found no significant difference in the mean GRT for individuals in upright, ambulatory and supine state. In the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions, and the floating units remained away from the pylorus. However, in supine position, the floating units are emptied faster than the non-floating units of similar size.

4. Concomitant drug administration

Administration of drugs with impact on gastrointestinal transit time for example drugs acting as anticholinergic agents (e.g. atropine, propantheline), opiates (e.g. codeine) and prokinetic agents (e.g. metoclopramide, cisapride) can alter gastro retention of oral dosage forms. Anticholinergics like atropine and propantheline increase gastric residence time. Drugs like metoclopramide and cisapride decrease gastric residence time.

5. Disease state

In gastric ulcer, diabetes, and hypothyroidism there is an increase in gastric residence time. In the case of hyperthyroidism and duodenal ulcers there is a decrease in gastric residence time.

Volume of the GI fluid

The resting volume of the stomach is 25 to 50 ml. The volume of liquids administered affects the gastric emptying time. When the volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids.

Effect of gastrointestinal fluid

On comparison of the floating and non-floating units, it was concluded that regardless of their sizes the floating units remained buoyant on the gastric contents throughout their residence in the GIT, while the non-floating units sink and remained in the lower part of the stomach. Floating units away from the gastro-duodenal junction were protected from the peristaltic waves during the digestive phase while non-floating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase.

Approaches of gastric retention[4,6]

To improve the retention of an oral dosage form in the stomach various approaches have been developed, e.g. high density systems, swelling and expanding systems, bioadhesive systems, altered density systems and other delayed gastric emptying devices.

A systematic flowchart of the approaches is shown in figure 5. Different approaches of gastroretention were described below and shown in figure 6.

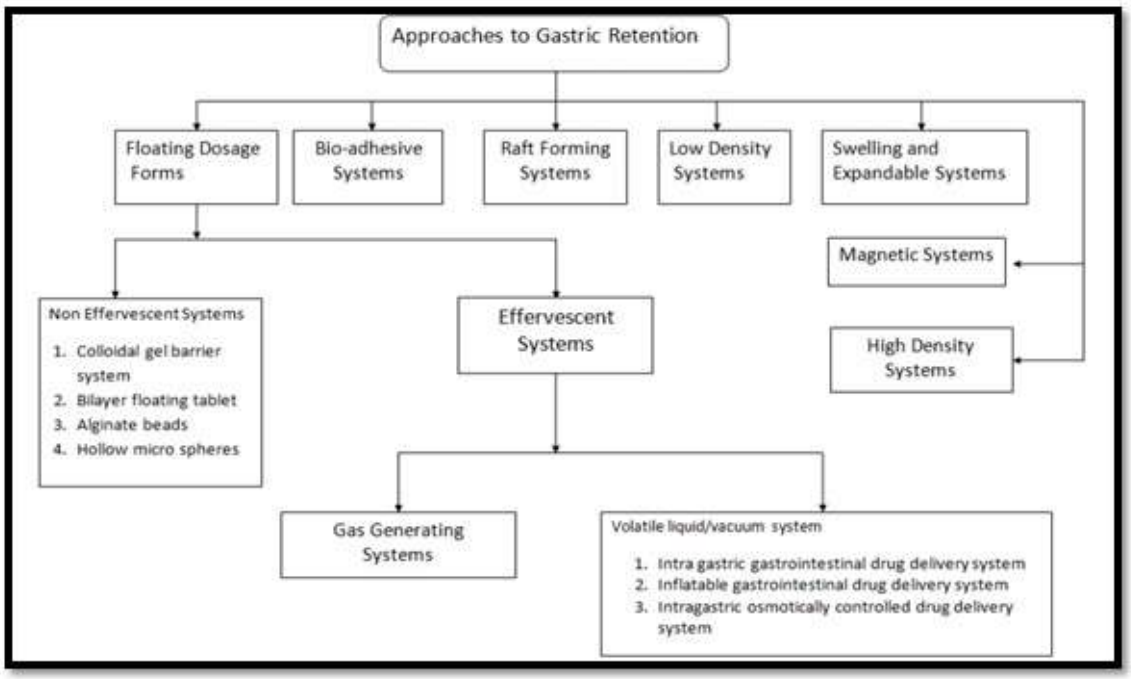

Figure 5: A systematic flowchart of the approaches

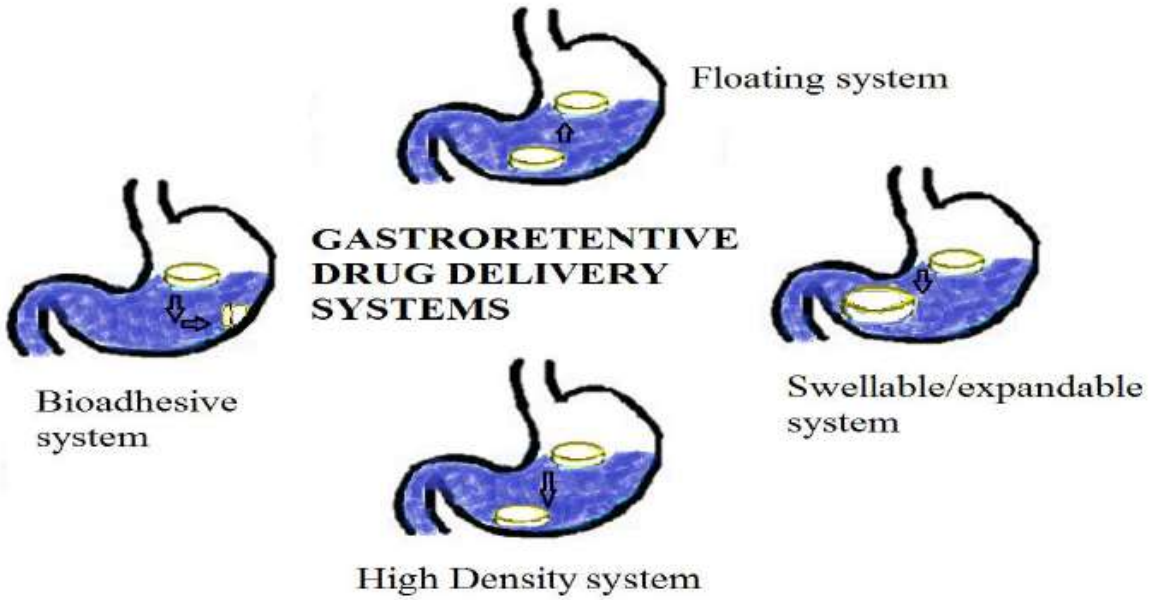

Figure 6: Approaches of gastroretentive drug delivery system.

High Density Sinking System

These systems with a density of about 3 g/cm3 are retained in the antrum part of the stomach and are capable of withstanding its peristaltic movements. The only major drawbacks with such systems is that it is technically difficult to manufacture such formulations with high amount of drug (>50%) and to achieve a density of about 2.8 g/cm3.

Low Density Floating System:-

Floating drug delivery systems (FDDS) or hydro dynamically balanced systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the stomach. After the release of the drug, the residual system is emptied from the stomach.

Mucoadhesive System

These are developed to perform drug absorption in a site specific manner. In this approach, bioadhesive polymers are used that adhere to mucosal epithelial surface in stomach, thereby increase gastric retention time.

Various mechanisms of adhesion are -

- Wetting theory, ability of bioadhesive polymers to spread and cause intimate contact with mucin layers.
- Diffusion theory, physical entanglement of mucin strand with soluble polymer or interpenetration of mucin strand into structure of polymer.
- Absorption theory, bioadhesion is due to secondary forces such as Vander walls forces and hydrogen binding.
- Electronic theory, proposes attractive electrostatic forces between glycoprotein mucin network and bioadhesive material.

Bioadhesive polymers used are - PAA, Chitosan, Sodium alginate, HPMC, Sucralfate, Tragacanth, Dextrin, PEG.

Limitation - Bioadhesion is difficult to maintain due to rapid turnover of mucin in GIT.

Swelling System

These are the dosage forms, which after swallowing, swells to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer period of time. These systems may be named as ‘plug type systems’, since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18mm in their expanded state. The balance between the extent and duration of swelling is maintained by the

degree of crosslinking between the polymeric chains. A high degree of cross – linking retards the swelling ability of the system maintaining its physical integrity for prolonged period.

Super Porous Hydrogel System

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

Magnetic System

Dosage forms contain a small internal magnet and a magnet is placed in abdomen over the position of stomach that retains dosage form in gastric region.

Disadvantage: -

• External magnet needs to be positioned with degree of precision.

• Patient non compliance

• Not very used.

Commonly used drug in formulation of gastro retentive dosages forms and marketed formulation[7]

Commonly used drugs in formulation of gastroretentive dosage forms and some gastroretentive products available in the market are listed in Table 1 and Table 2 respectively.

Table 1: Commonly Used Drugs In Formulation Of Gastroretentive Dosage Forms

Dosage forms	Drugs
Floating Tablets	Acetaminophen, Acetylsalicylic acid,Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbid mononitrate, p-Aminobenzoic acid(PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil
Floating Capsules	Chlordiazepoxide HCl, Diazepam, Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin
Floating Microspheres	Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast
Floating Granules	Diclofenac sodium, Indomethacin, Prednisolone
Powders	Several basic drugs
Films	Cinnerzine

Table 2: Gastroretentive products available in the market

Brand Name	Active Ingredient(s)
Cifran OD ®	Ciprofloxacin
Madopar ®	L-DOPA and Benserazide
Valrelease ®	Diazepam
Topalkan ®	Aluminum -magnesium antacid
Almagate FlatCoat ®	Aluminum -magnesium antacid
Liquid Gavison ®	Aluminium hydroxide,
Conviron	Ferrous sulfate
Cytotec®	Misoprostal

Evaluation

A. *In-vitro* Evaluation Methods

Fourier Transform Infrared Spectroscopy

Fourier transform infrared spectroscopy is mostly used to identify organic, polymeric, functional group and some inorganic materials as well. FT-IR measurement of pure drug, polymer and drug loaded formulations are obtained by using FT-IR technique. The pellets are prepared on KBR press under hydraulic pressure of 150kg/cm2 and spectra are scanned over the wave number range of 3600-400cm-1 at ambient temperature[8].

Differential Scanning Calorimetry

DSC is performed to characterize water of hydration of pharmaceuticals. Thermo grams of formulated preparations are obtained using DSC instrument. The sample preparations are sealed in aluminum pan and heated at a constant rate of 10ºC/min over a temp range 25ºC-65ºC[8].

Particle Size Analysis and Surface Characterization

(For floating microspheres and beads)

By using optical microscopy method particle size and size distribution of beads or microspheres are determined in the dry state. The morphology (external and cross sectional) is done by scanning electron microscope[8].

Determination of Drug Content

Percentage drug content gives how much amount of drug is present in the formulation. It should not exceed the limit acquired by the monograph. It can be using HPLC, HPTLC methods, micro titrimetric method and also by using spectroscopy techniques[8].

Dissolution Studies

The dissolution test is generally performed for calculating the amount of drug release using USP dissolution test apparatus. Generally, test is performed using 900ml of 0.1 N HCL, at 37ºC and 100 rpm and sample of 10 ml is withdrawn hourly and analyzed under U.V. and absorbance is

measured. The sample is replaced by the dissolution media. Cumulative percentage is calculated using equation obtained from standard curve[8].

Floatation Studies

The *in-vitro* buoyancy is characterized by floating lag time and total floating time. The floating lag time and total floating time are measured by placing the dosage form in a 250 ml beaker containing 200ml of 0.1N HCL. The time required by the dosage form to come to surface and float is known as floating lag time and the time period upto which the dosage form remained buoyant is called total floating time[8].

Swelling Index

After immersion of swelling dosage form into SGF at 37^0C, dosage form is removed out at regular interval and dimensional changes are measured in terms of increase in tablet thickness / diameter with time[9].

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. So it is also termed as Weight Gain[9].

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

Where,

Wt = Weight of dosage form at time t

Wo = Initial weight of dosage form

***In-vivo* evaluation methods**

X-ray

It helps to locate dosage form in the GIT by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. The inclusion of a radio opaque material into solid dosage form enables it to be visualized by the X-ray[8]. Most commonly used radio opaque marker is Barium Sulphate[10].

Gamma scintigraphy

The inclusion of a gamma emitting radionuclide in the formulation allows indirect external observation using gamma camera, the gamma rays emitted by radionuclide is focused on the camera which helps to monitor the location of the dosage form[8]. Widely used emitting material is 99Tc[10].

Gastroscopy

It comprises of peroral endoscopy used with a fiber optic and video system. It is used to inspect

visually the effect of prolonged stay in stomach milieu on the floating drug delivery system[8].

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 this method is radiation less and hence not hazardous[10].

$_{13}$C Octanoic Acid Breath Test

$_{13}$C Octanoic acid is incorporated into GRDDs. In stomach due to chemical reaction, octanoic acid liberates CO_2 gas which comes out in breath. The important Carbon atom which will come in CO_2 is replaced with $_{13}$C isotope. So time up to which $_{13}CO_2$ 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 CO_2 release. So this method is cheaper than other[10]

CONCLUSION

This article provides detailed information on gastroretentive drug delivery system including its evaluation. By looking towards various literature surveys it can be concluded that drug absorption in the gastrointestinal tract is variable process and by using gastroretentive approach one can extend time for drug absorption. Hence this gastroretentive drug delivery system can provide additional advantage to those drugs which are absorbed primarily from upper part of gastrointestinal tract. Also, we can improve bioavailability of those drugs which exhibit site specific absorption. Different approaches of gastroretention have its own merits and demerits, but to achieve proper gastroretention we can try combined approaches.

CONFLICT OF INTEREST

"The author(s) declare that they have no competing interests".

REFERENCES

1. Saravanana M, Anupama B. Development and evaluation of ethyl cellulose floating microspheres loaded with ranitidine hydrochloride by novel solvent evaporation-matrix erosion method. Carbohydrate Polymers 2011; 85:592–598.
2. Dutta P, Sruti J. Floating Microspheres: Recent Trends in the Development of Gastroretentive Floating Drug Delivery System. Int J Pharma Sci Nanotechnology 2011; 4(1):1296-1306.
3. Brahmankar D, Jaiswal S. Biopharmaceutics and Pharmacokinetics - A Treatise 2nd ed., Vallabh Prakashan:448.
4. Kajale A, Chandewar A. Recent Advancement in Gastro Retentive Drug Delivery System – A Review. Indo Am J Pharma Res 2013; 3(7): 5221-5232.

5. Prajapati V, Jani G, Khutliwala T, Zala B. Raft forming system-An upcoming approach of gastroretentive drug delivery system. J Controlled Release 2013; 168:151-165.
6. Swetha S, Allena R and Gowda D.V. A Comprehensive Review on Gastroretentive Drug Delivery Systems, Int J Res Pharma Biomedical Sci 2012; 3 (3):1285- 1293.
7. Nayak A, Maji R, Das B, Gastroretentive drug delivery systems: a review, Asian Journal of Pharmaceutical and Clinical Research. 2010;3(1):2-10.
8. Sharma D., Sharma A., Gastroretentive drug delivery system - a mini review. Asian Pac. J. Health Sci., 2014; 1(2): 80-89.
9. Kumar S., Jamil F., Rajput M., Sharma S. Gastro Retentive Drug Delivery System: Features and Facts, Int J Res Pharma Biomedical Sci 2012; 3(1):125-136.
10. Shaik T, Sundaram M, Umasankar K. Review On Gastroretentive Drug Delivery System, International Journal of Research in Pharmaceutical and Nano Sciences. 2014; 3(3):177 - 185.
11. Allamneni Y, Reddy B. Performance Evaluation of Mucoadhesive Potential of Sodium Alginate on Microspheres Containing an Anti-Diabetic Drug: Glipizide. Int J Pharma Sci Drug Res 2012; 4(2): 115-122.
12. Amrutkara P, Chaudharib P, Patil S. Design and in vitro evaluation of multiparticulate floating drug delivery system of zolpidem tartarate. Colloids and Surfaces B: Biointerfaces 2012; 89:182-187.
13. Dixit N. Floating Drug Delivery System. J Current Pharma Res. 2011; 7 (1): 6-20.
14. Mayavanshi A, Gajjar S. Floating drug delivery systems to increase gastric retention of drugs: A Review. Res J. Pharm. and Tech.2008; 1(4):345-348.
15. Patil J, Kamalapur M. Ionotropic Gelation and Polyelectrolyte Complexation: The Novel Techniques to Design Hydrogel Particulate Sustained, Modulated Drug Delivery System: A Review. Digest J Nanomaterials and Biostructures 2010; 5(1): 241-248.
16. Tetsuo A, Kazuhide H. 15th Anniversary of Rebamipide: Looking Ahead to the New Mechanisms and New Applications, Digestive Diseases and Sciences. 2005; 50:S3–S11.
17. Toshio W, Kazuhide H, Koichi T. Rebamipide Reduces Delay in Gastric Ulcer Healing in Cyclooxygenase-2-Deficient Mice, Digestive Diseases and Sciences. 2005; 50:S63–S69.
18. Khirwadkar P, Dashora K. Gastroretentive dosage forms: current developments in novel system design and evaluation. Am J Pharmtech Res 2011; 1(3):57-87.

19. Mali A, Bathe R. A Review on Gastroretentive Floating Drug Delivery System. Am J Pharmtech Res 2015; 5(2):108-132.