International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 891-903 www.ijprajournal.com ISSN: 2249-7781

Gastroretentive Floating Drug Dilivery System:A Review

Abhishek yadav, Mrs. Surinder Kaur, Dr. Gururaj Kulkarn, Dr. Padma M Paarakh

Department Of Pharmaceutics , The Oxford College Of Pharmacy ,Bangalore ,Karnataka 56008, INDIA

Date of Submission: 30-07-2021 Date of Acceptance: 08-08-2021

I. INTRODUCTION

In the past few years, significant medical advances have been made in the area of drug delivery with the improvement of novel dosage forms. The area of sustained drug delivery has graduated from being merely a research item to a commercialy viable product. An appropriately designed sustained release drug delivery system can be a major progress towards solving problems concerned with the direction of a drug to a specific organ or tissue and controlling the rate of drug delivery.

The term "optimization" is often used in pharmacy related to formulation as well as processing, and one will find it in the literature referring to any study of the formula.Drug products are frequently developed by an effective compromise between competing characteristics to attain the best formulation and process within a given set of restrictions.

Due to the various benefits like formulation flexibility, ease of administration and patient compliance the oral drug delivery is still the most preferable route of administration. A gastric floating drug delivery system (GFDDS) is particularly useful for drugs that have an absorption window in a specific region of the gastrointestinal tract that is in the duodenum and upper jejunum segments. This system prolongs the retention time of the oral dosage form in the stomach thus improving the oral bioavailability of the drug, prolonging dosing intervals and increased patient compliance. Such retention systems are useful for those drug that get degraded in the intestine like antacids, certain antibiotics and enzymes that act locally in the stomach etc.(1,2)

Some drugs get destroyed in the alkaline pH, to overcome this, gastro retentive dosage forms can be formulated using hydrophilic polymer that slowly form thick gel, which retains integrity of the formulation and stimulates the drug release through thick gel and controls the burst release.The gelatinous polymer barrier formation results from hydrophilic polymer swelling. Drug is released by diffusion and erosion of the gel barrier. [3]

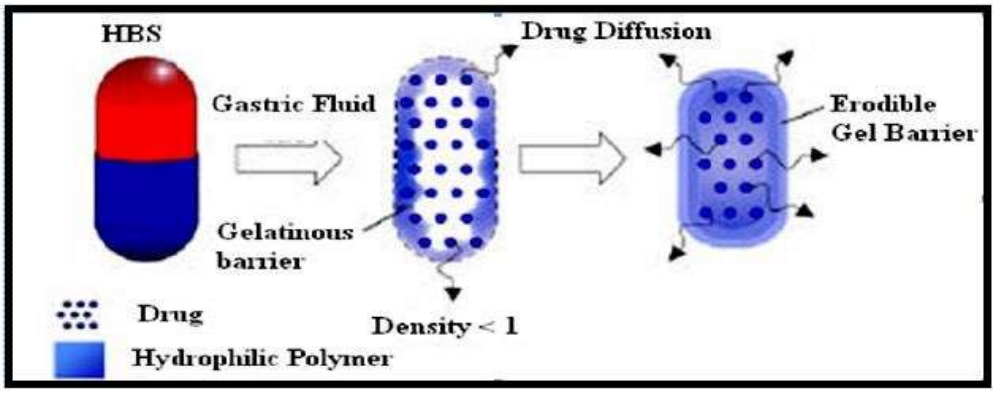

Figure 1:- Hydrodynamically balanced system (HBS)

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 891-903 www.ijprajournal.com ISSN: 2249-7781

Floating drug delivery system also known as hydro dynamically balanced system, have a bulk density lesser than gastric fluids and hence remain buoyant in the gastric fluids for a prolonged period of time without affecting the gastric emptying rate. Although the system is floating on the gastric content, the drug is released slowly at desired rate from the system. Hydrodynamically balanced drug delivery system, in either tablet or capsule form, is designed to prolong gastrointestinal (GI) residence time in the area of gastro intestinal tract. [4]

Numerous approaches are currently used to retain the dosage form in the stomach which include bioadhesive systems, swelling and expanding systems, floating systems and other delayed gastric emptying devices.A few of them have been exemplified here:

A) **High-density systems** having density of ~3 g/cm^3 are retained in the rugae of the stomach. The only major drawbacks with such systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and to achieve the required density of 2.4–2.8 g/cm^3.[5,6]

B) **Swelling systems** are capable of swelling to a size that prevents their passage through the pylorus as a result, the dosage form is retained in the stomach for a longer period of time upon coming in contact with gastric fluid, and the polymer imbibes water and swells.[7]

C) **Bio/mucoadhesive systems** to the gastric epithelial cell surface or mucin extend the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The epithelial adhesive properties of mucin have been applied in the development of Gastro retentive drug delivery systems.[8]

D) **Low-density** systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period.

Each delivery system was aimed at cyclic changes in plasma concentration seen after the administration of a conventional delivery system.[2,9]

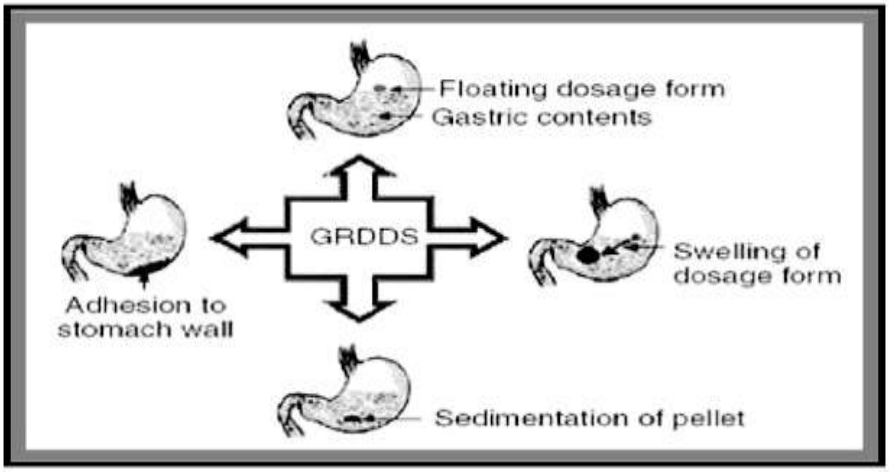

Figure2 :- Different approaches of gastric retention

Other systems such as:

Sustained release:

It indicates an initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release over an extended period.

Controlled release:

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 891-903 www.ijprajournal.com ISSN: 2249-7781

These dosage forms release drug at a constant rate and provide plasma concentrations that remain invariant with time.

Delayed release:

It indicates that the drug is not being released immediately following administration but at a later time, e.g. enteric coated tablets, pulsatile-release.

Repeat action:

It indicates that an individual dose is released rapidly after administration, and second or third doses are subsequently released at intermittent intervals.

Prolonged release:

It indicates that the drug is provided for absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slow release rate from the dosage form.

Extended release:

Certain dosage forms release drug slowly, so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 and 12 hours). [10]

When conventional immediate release dosage forms are administered on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys associated with administration of each dose, however, when dose are not administered on schedule, the resulting peaks and valleys reflects less than optimum drug therapy. For example, if doses are administered too often, minimum toxic concentration (MTC) of drug may reach, with resulting toxic side effects. If doses are missed, periods of sub-therapeutic drug blood levels or those below the minimum effective concentration (MEC) may result,with no benefit to the patient.Multiple daily dosing is inconvenient for the patient and can result in missed doses made-up doses and noncompliance with the regimen. The sustained plasma drug level provided by extended-release often eliminates the need for night dosing, which benefits not only the patient but the caregiver as well.

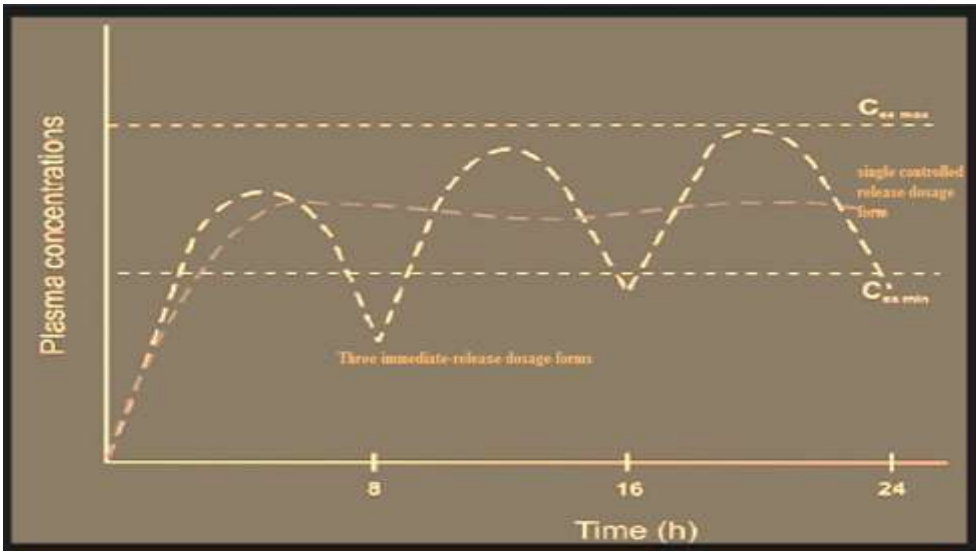

Figure3 :- Schematic presentation of plasma concentration-versus-time profile following administration of three immediate-release dosage forms versus one single controlledrelease dosage form.

Controlled released dosage forms release drug at a constant rate and provide plasma concentrations that remain invariant with time and Sustained released dosage forms designates an initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release over an extended period compared to conventional dosage forms. (Figure:-4)

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 891-903 www.ijprajournal.com ISSN: 2249-7781

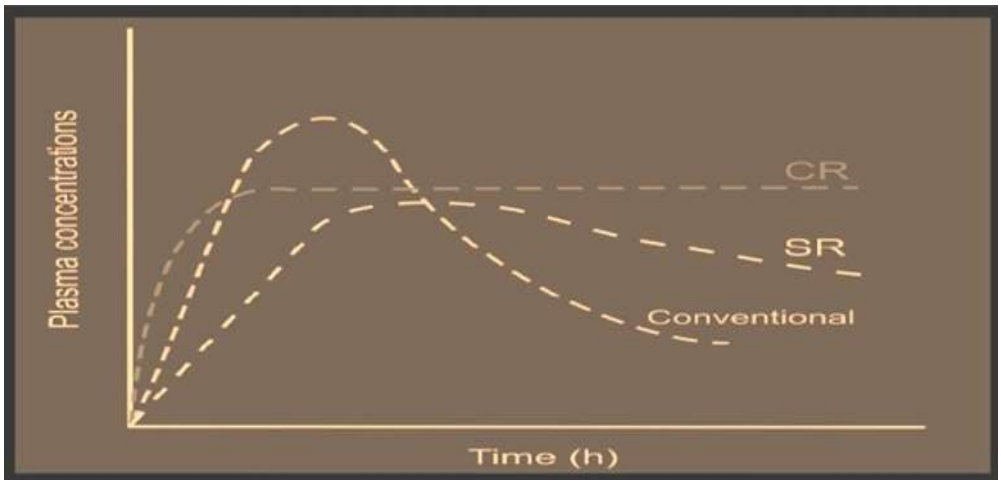

Figure4:- Schematic presentation of plasma concentration-versus-time profiles following administration of controlled release (CR), sustained release (SR), and conventional dosage form.

Mechanisms of Drug Release from Oral Controlled Delivery Systems

1. **Dissolution controlled release**
a) Matrix dissolution control
b) Reservoir dissolution control
2. **Diffusion controlled release**
a) Matrix diffusion control
b) Reservoir diffusion control
3. **Osmotic controlled release**
4. **Ion exchange resins**
5. **Regulated systems**
6. **Gastro retentive systems**

1. Dissolution controlled release:

Dissolution controlled release can be obtained by slowing down the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness.

(a) Matrix dissolution control:

In these systems, the drug is homogeneously dispersed throughout a rate controlling membrane. The drugs which are highly water soluble can also be formulated as controlled release products by controlling their dissolution rate using slowly soluble polymers.

(b) Reservoir dissolution control

In reservoir dissolution controlled system the drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose derivates, polyethylene glycols, polymethacrylate, waxes etc.

2. Diffusion controlled release:

Diffusion of a drug molecule through a polymeric membrane forms the basis of this controlled drug delivery system. Similar to the dissolution controlled devices, these are manufactured either by encapsulating the drug particle in a polymeric membrane.

(a) Matrix diffusion control

Matrix devices are very common because of ease of fabrication. Diffusion controlled involves dispersion of drug in either water-insoluble or a hydrophilic polymer.

(b) Reservoir diffusion control

A core of drug is coated with the water insoluble polymer. The polymer can be applied by coating or microencapsulating technique. The drug release mechanism across the membrane involves diffusion of dissolution media through the membrane to the inside of the core, then dissolution of the drug and diffusion of the drug into the surrounding fluid. Materials used in such devices are hydroxyl propyl cellulose, ethyl cellulose and polyvinyl acetate.

3. Osmotic controlled release:

The oral osmotic pump is based on the principle of osmotic pressure which releases the drug at constant rate. The dosage form contains a small hole from which the dissolved drug moves out at a rate determined by the rate of entrance of water due to osmotic pressure. The rate of release is constant and can be controlled within tight limits yielding relatively constant blood concentrations

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 891-903 www.ijprajournal.com ISSN: 2249-7781

4. Ion exchange resins:

Drugs can be bound to ion exchange resins and when ingested, the ionic environment within the GIT determines the release of the drug. The drug is released slowly by diffusion mechanism from the resins particle structure. Examples of these types of products are Duromine containing the basic drug phentermine complex onto an anionic resin and MS Contain (morphine sulphate) suspension which uses a polystyrene sulphonate resin.

5. Regulated systems:

These devices are capable of releasing therapeutic agents by well-defined kinetics and have significant improvement over conventional controlled release systems. For example, control of diabetes is achieved by delivering insulin in response to blood glucose levels. But self-regulated devices can act without external intervention. The response to changes in temperature or pH within the system leads to drug release. An example of this type of system is insulin release from pH sensitive polymers.

6. Gastroretentive systems:

Variability in GI transit time is a concern for oral controlled drug delivery system. Drugs with a narrow absorption window in the GI tract are particularly susceptible to variation in both bioavailability and times to achieve peak plasma levels. Gastroretentive controlled release formulations could offer a potential solution to the problem by offering a prolonged gastric residence time. Gastroretentive delivery systems (GRDS) are beneficial for such drugs by improving their bioavailability, therapeutic efficacy and by possible reduction of dose.

This approach is deal with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. (11)

GASTRIC EMPTYING

Apart from dissolution of a drug and its permeation through the biomembrane, the passage from stomach to small intestine, called as gastric emptying, can also be a rate-limiting step in drug absorption.

Factors Affecting the Gastric Emptying

1. Size, shape and density of the dosage form.
2. Concomitant ingestion of the food and its nature, caloric content and frequency of intake.
3. (Simultaneous) administration of drugs acting as anti-cholinergic agent (e.g.Atropine, Propentheline), opioids (e.g. Codeine) and prokinetic agents (e.g. Metoclopromide, Isapride).
4. Biological factor such as gender, posture, age, sleep, body weight, physical activity and Disease states (e.g. diabetes, crohn's disease).

Furthermore, the relatively brief gastric emptying time in humans which normally averages 2-3h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose.Normal gastric residence time usually range approximately between 5 minutes and 2 hours.

Migrating myoelectric complex (MMC) is responsible for gastric emptying that is characterized by four phases:

Phase I – Period of no contraction (30-60 minutes)

Phase II – Period of intermittent contractions (20-40 minutes)

Phase III – Period of regular contractions at the maximal frequency that travel distally also known as housekeeper wave. (10-20 minutes) and

Phase IV - Period of transition between phase III and phase I (0-5 minutes).(12)

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 891-903 www.ijprajournal.com ISSN: 2249-7781

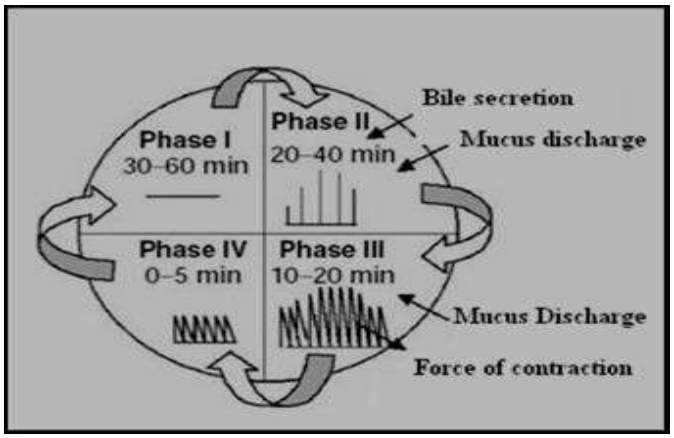

Figure 5:- Schematic representation of inter-digestive motility

FLOATING DRUG DELIVERY SYSTEM

Floating Drug Delivery System (FDDS) are retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. Floating drug delivery system (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.[13]

A. Single unit floating system

a) Noneffervescent system

Hydrodyanamic balanced systems

Sheth and Tossounian first designated this 'hydrodynamically balanced system'. Such a 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 . On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloid gel barrier around its surface. [5]

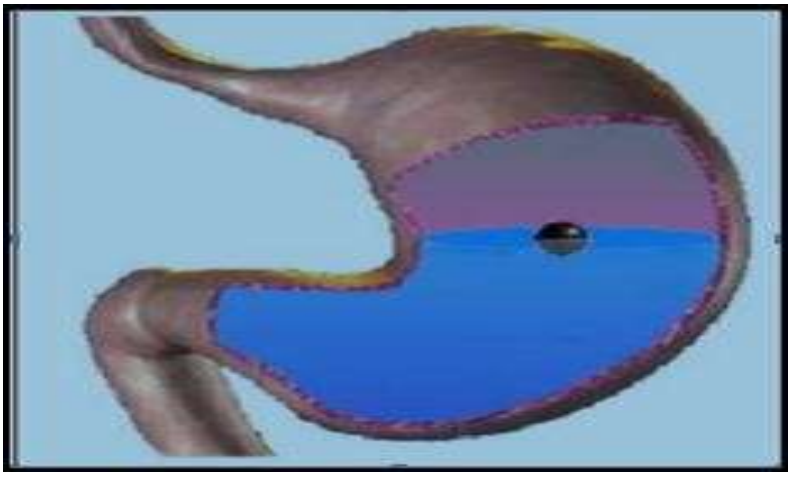

Figure 6:- Intra-gastric residence position of floating unit

Floating chamber

Fluid-filled floating chamber [14] includes incorporation of a gas-filled floatation chamber into a micro porous component that houses a drug reservoir. Openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The device is of swallowable size, remains float within the stomach for a prolonged time, and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 891-903 www.ijprajournal.com ISSN: 2249-7781

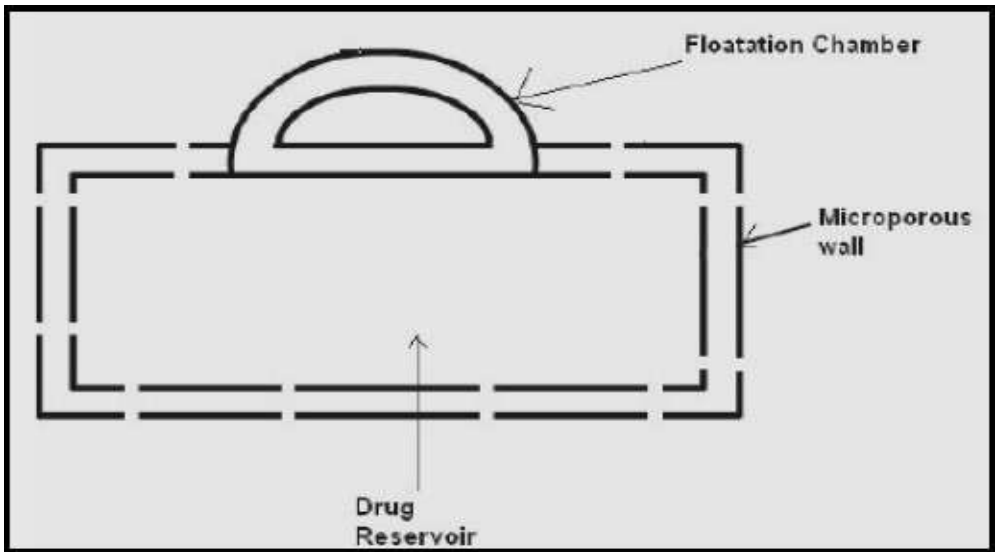

Figure 7:- Gas filled floatation chamber Tablets

Tablets with Hollow Cylinder

A new floating device consists of two drug-loaded HPMC matrix tablets, placed within an open impermeable, hollow polypropylene cylinder. Each matrix tablet closes one of the ends of the cylinder so that an air-filled space is created between them, which in turn provided a low, overall density of the system. The device should remain floating until at least one of the tablets has dissolved. [15]

Multilayer Flexible Film

This device is multilayered, flexible, sheet like medicament device that was buoyant in the gastric juice of the stomach and had sustained release characteristics. The device consisted of self-supporting carrier film(s) made up of a water insoluble polymer matrix with the drug dispersed there in, and a barrier film overlaying the carrier film. The barrier film consisted of a water insoluble and a water and drug permeable polymer or copolymer. Both films were sealed together along their periphery, in such a way as to entrap a plurality of small air pockets, which imparted the laminated films their buoyancy. The time for buoyancy and the rate of drug release can be modulated by the appropriate selection of the polymer matrix. [16]

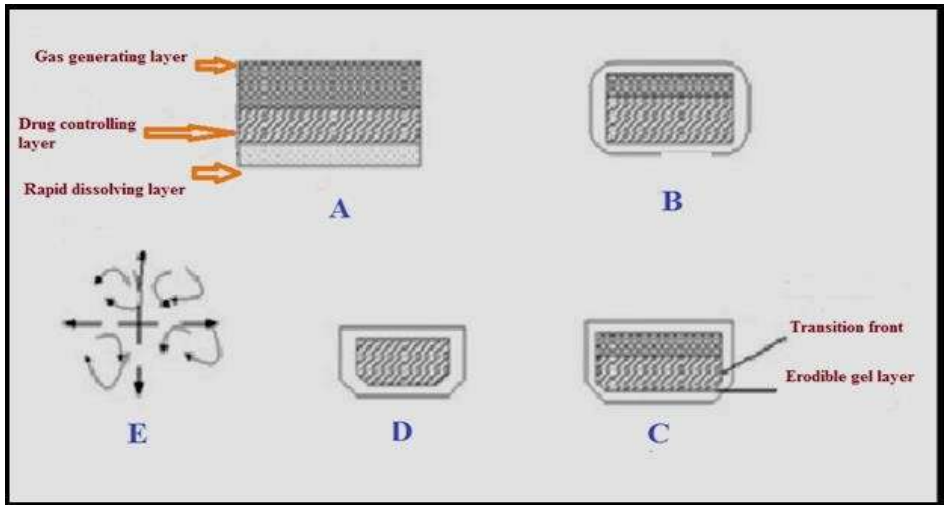

Figure 8:- Schematic presentation of working of a triple-layer system. (A) Initial configuration of triple-layer tablet. (B) On contact with the dissolution medium the bismuth layer rapidly dissolves and matrix starts swelling. (C) Tablet swells and erodes. (D) And (E) Tablet erodes completely

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 891-903 www.ijprajournal.com ISSN: 2249-7781

b) Effervescent Floating Dosage Forms (Gas Generating Systems):

Floating systems containing effervescent components

These are matrix type of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen hydrocolloids, which provide buoyancy to the dosage forms. In vitro, the lag time before the unit floats is <1 min and the buoyancy is prolonged for 8 to 10 h (Figure: - 9). In vivo experiments in fasted dogs showed a mean gastric residence time increased up to 4 h. compressing the gas generating components in a hydrocolloid containing layer and the drug in another layer formulated for a sustained release effect, thereby producing a bilayer tablet. [17]

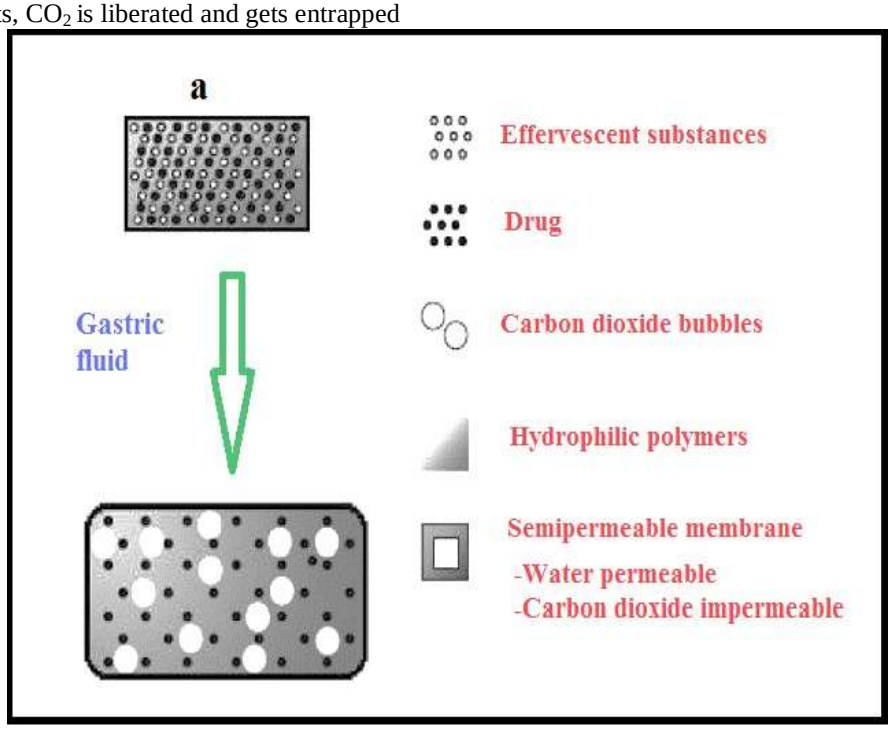

Figure 9:- Gas generating system: schematic monolayer drug delivery system

Floating System Based On Ion Exchange Resin

The resin beads were loaded with bicarbonate and theophylline which were bound to the resin. The loaded resin beads were coated with a semi permeable membrane to overcome rapid loss of CO_2. After exposure to gastric media, exchange of bicarbonate and chloride ions took place and lead to the formation of CO_2, which was trapped within the membrane, causing the particles to float.

Floating system with inflatable chamber

An alternative mechanism of gas generation can be developed as an osmotically controlled floating device, where gases with a boiling point < 37°C (e.g. cyclopentane, diethyl ether) can be incorporated in solidified or liquefied form into the systems. At physiological temperatures, the gases evaporate enabling the drug containing device to float. [18]

Programmable drug delivery

A programmable, controlled release drug delivery system has been developed in the form of a non-digestible oral capsule (containing drug in a slowly eroding matrix for controlled release) was designed to utilize an automatically operated geometric obstruction that keeps the device floating in the stomach and prevents it from passing through the remainder of the GIT.

The duration during which the device could maintain its geometric obstruction (caused by a built-in triggering ballooning system) was dependent on the erosion rates of the incorporated polymers (the capsule in-hosed core matrix). After complete core matrix erosion, the ballooning system is automatically flattened off so that the device retains its normal capsule size to be eliminated by passing through the GIT. [19]

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 891-903 www.ijprajournal.com ISSN: 2249-7781

B. Multiple unit floating system

a) Non-effervescent Systems:

Alginate beads

Alginates are nontoxic, biodegradable linear copolymers composed of Lglucuronic and L-mannuronic acid residues. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at -40°C for 24 hours,leading to the formation of porous system, which can maintain a floating force over 12 hours. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. [20]

b) Effervescent systems:

Floating pills

Floating pill composed of effervescent layers and swellable membrane layers coated on sustained release pills. The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into 2 sub layers to avoid direct contact between the 2 agents. This is surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, produce swollen pills (like balloons) with a density less than 1.0 g/ml due to incorporation of CO_2.[21] (Figure: - 10)

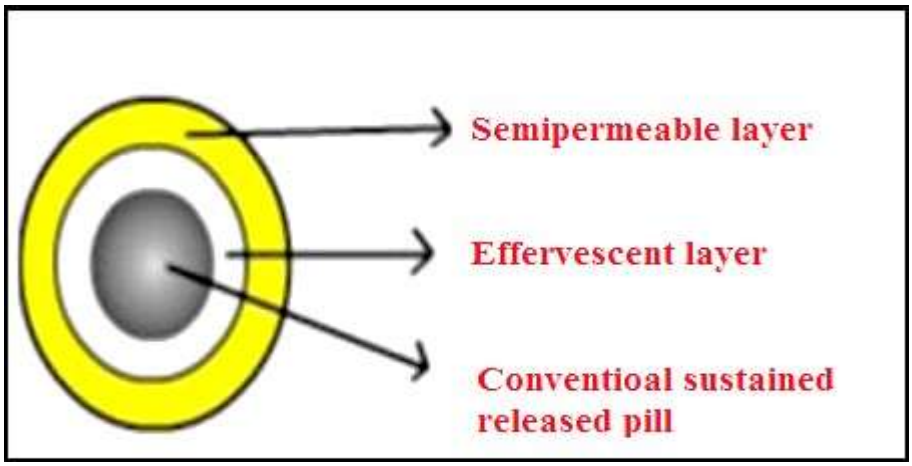

Figure 10:- (A) Multiple-unit oral floating drug delivery system

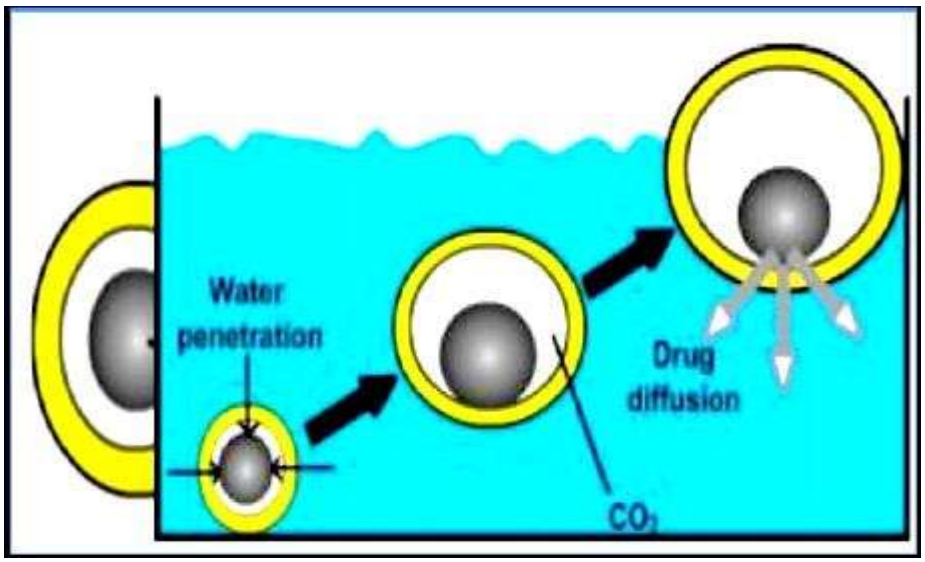

Figure :- 10 (B) Working principle of effervescent floating drug delivery system

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 891-903 www.ijprajournal.com ISSN: 2249-7781

C) Hollow Microspheres:

Hollow microspheres are considered as one of the most promising buoyant systems , as they possess the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere . Buoyancy and drug release are dependent on quantity of polymer, the plasticizer–polymer ratio and the
solvent used. (22, 23)

D. Raft forming system [24]

On contact with Gastric fluid a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles. Such formulation typically contains antacids such as Aluminium Hydroxide or Calcium Carbonate to reduce gastric acidity. They are often used for gastro esophageal reflux treatment as with Liquid Gaviscon (GlaxoSmithKline) (Figure:-12).

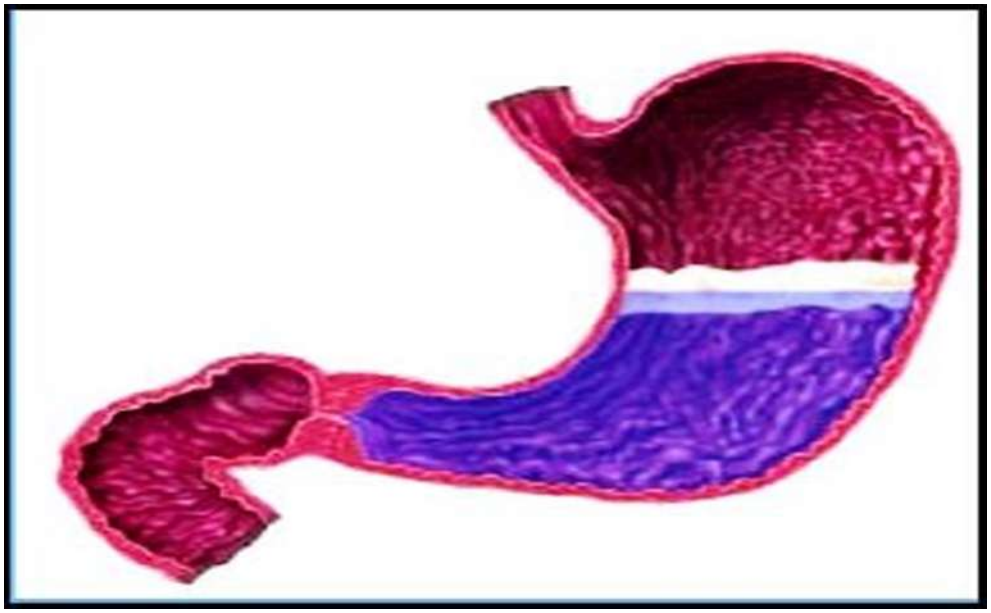

Figure 11:- Barrier formed by a raft-forming system

FACTORS AFFECTING THE FLOATING AND FLOATING TIME

1. **Density:** - Floating is a function of dosage form buoyancy that is dependent on the density.
2. **Shape of dosage form:** - Tetrahedron and ring shaped devices with flexural modules of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better floating, 90% to 100% retention at 24 hours compared with other shapes. [25]
3. **Concomitant drug administration:** - Anti-cholinergics like atropine and propantheline,opioids like codeine and prokinetic agents like metoclopramide and cisapride; can affect floating time.
4. **Fed or unfed state:** - Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. (26)
5. **Nature of meal:** - 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 and feeding frequency:** - Floating can be increased by four to 10 hours with a meal that is high in proteins and fats. The floating can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
7. **Age:** - Elderly people, especially those over 70, have a significantly longer floating. [27] Disease Condition such as diabetes and Crohn's disease etc. also affect drug delivery.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 891-903 www.ijprajournal.com ISSN: 2249-7781

8. **Posture: -** Floating can vary between supine and upright ambulatory states of the patient. [28]

ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM [2, 29]

I. The principle of floating drug delivery system can be used for any particular medicament or class of medicament.

II. The Floating drug delivery system are advantageous for drugs absorbed through the stomach e.g. ferrous salts and for drugs meant for local action in the stomach and treatment of peptic ulcer disease e.g. antacids.

III. The efficacy of the medicaments can be increased utilizing the sustained release.

IV. When there is vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected under such circumstances it may be advantage drug in floating condition in stomach to get a relatively better response.

V. Floating drug delivery provides advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region.

VI. The Floating drug delivery formulations are not restricted to medicaments, which are principally absorbed from the stomach. Since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine e.g.

Chlorpheniramine maleate.

Certain types of drugs are beneficial as FDDS. These include:

a) Drugs acting locally in the stomach.
b) Drugs those are primarily absorbed in the stomach.
c) Drugs those are poorly soluble at an alkaline.
d) Drugs with a narrow window of absorption.
e) Drugs absorbed rapidly from the GI tract.
f) Drugs those degrade in the colon.

DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM [30]

1. There are certain situations where gastric retention is not desirable. Aspirin and nonsteroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted.
2. Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in Gastro retentive systems.
3. Furthermore, other drugs, such as iso-sorbidedinitrate, that are absorbed equally well throughout the GI tract, drugs undergoing first pass metabolism will not benefit from incorporation into a gastric retention system.
4. It requires sufficient high level of fluids in the stomach for the drug delivery to float.
5. The dosage form should be administered with a full glass of water

Evaluation studies for floating tablet formulation

a) Precompressionparameters

- BulkDensity
- TappedDensity
- Angle ofRepose
- Carr'sIndex
- Hausner'sRatio

b) Physico-chemicalcharacteristicsofcompressedFloatingtablets

- Weightvariation
- Thickness
- Hardness
- Friability
- Floating lagtime
- Total buoyancytime
- Drug contentanalysis

c) In-Vitro drugrelease

- Tablet dissolutionprofile

II. CONCLUSION:

The gastro retentive floating drug delivery system is prepared in an effort to increase the gastric retention time of the dosage form and to control drug release. One of the most feasible approaches for achieving a prolonged and predictable dug delivery profiles in the gastrointestinal tract is to control the gastric residence time, using gastro-retentive dosage forms that will provide us with new and important therapeutic options. Floating matrix tablets are designed to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 891-903 www.ijprajournal.com ISSN: 2249-7781

companies are focusing toward commercializing this technique.

REFERENCE

[1]. Moes J. Gastroretentive dosage forms. Crit Rev Ther Drug Carrier Syst 1993;10:143-
[2]. 59.
[3]. Deshpande A, Shah N, Rhodes C, Malick W. Development of a novel controlled release system for gastric retention. Pharm Res 1997;14:815-9.
[4]. Seth PR, Tossounian J. The hydrodynamically balanced system-a novel drug delivery system for oral use. Drug DevInd Pharm 1984;10:313-39.
[5]. Baumgartner S, Kristl J, Vrecer F, Vodopivec P, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm 2000;195:125-
[6]. 35.
[7]. Bechgaard H., Ladefoged K. Distribution of pellets in the gastrointestinal tract: The influence on transit time exerted by density or diameter of pellets. J.PharmPharmacol 1978;30:690-2.
[8]. Davis S, Stockwell S, Taylor M, Hardy J, Whelley D. The effect on density on the gastric emptying of Single and multiple-unit dosage form. Pharm Res 1986;3:208-13.
[9]. Klausner A, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. J Control Release 2003;90:143-62.
[10]. Ponchel G, Irache J. Specific and nonspecific bioadhesive particulate system for Oral delivery to the gastrointestinal tract. Adv Drug Deliv Rev 1998 Dec 1;34(2-3):191-219.
[11]. Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y. Hallow microspheres for use as a floating controlled drug delivery system in the stomach. J Pharm Sci 1992 Feb;81(2):135-40.
[12]. Allen V, Popovich G, Ansel H. Pharmaceutical dosage forms and drug delivery systems.8$_{th}$ed. New Delhi: Wolters Kluwer; 2005. p. 260-72.
[13]. Aulton M. Pharmaceutics the science of dosage form design. 2$_{nd}$ ed. Edinburgh: Harcourt Publishers Limited; 2002. p. 290-95.
[14]. Wilson C G, Washington N. Physiological Pharmaceutics: Biological Barriers to Drug Absorption. Horwood Ellis Chichester; 1989. p. 47-70.
[15]. Singh B, Kim K. Floating drug delivery systems an approach to oral controlled drug delivery via gastric retention. J Control Rel 2000; 63:235-9.
[16]. Joseph NJ, Lakshmi S, Jayakrishnan A. A floating-type oral dosage form for piroxicam based on hollow polycarbonate microballoons: In vitro and in vivo evaluation in rabbits. J Control Release 2002; 79:71–9.
[17]. Krögel I, Bodmeier R. Floating or pulsatile drug delivery systems based on coated effervescent cores. Int J Pharm 2007;175-84.
[18]. Mitra SBW, MN. Sustained release oral medicinal delivery device. United States: Minnesota Mining and Manufacturing Company; 1984.
[19]. Ingani HM, Timmermans J, Moës AJ. Conception and in vivo investigation of peroral sustained release floating dosage forms with enhanced gastrointestinal transit. Int J Pharm 1987; 35:157-64.
[20]. Atyabi F, Sharma H, Mohammad H, Fell JT. Controlled drug release from coated floating ion exchange resin beads. J.Control.Release 1996;42:25-8.
[21]. Bashaw, Zaffaroni, Alejandro, Michaels, Alan S. Self-monitored device for releasing agent at functional rate. ALZA Corporation (Palo Alto, CA), United States.
[22]. Jain N. Progress in controlled and novel drug delivery systems. 1$_{st}$ed. New Delhi: CBS Publishers and Distributors; 2004. p. 84-5.
[23]. Iannuccelli V, Coppi G, Bernabei M, Cameroni R. Air compartment multiple-unit system for prolonged gastric residence. Int J Pharm 1998;174:47-54.
[24]. Ichikawa M, Watanabe S, Miyake Y. A new multiple unit oral floating dosage system. I:Preparation and in vitro evaluation of floating and sustained-release kinetics. J Pharm Sci1991;80:1062-6.
[25]. Sato Y, Kawashima Y, Takeuchi H, Yamamoto H. In vivo evaluation of riboflavin containing microballoons for floating controlled drug delivery system in healthy human volunteers.J Control Release 2003;93:39–47.
[26]. Washington N. Investigation into the barrier action of an alginate gastric reflux

suppressant, Liquid Gaviscon. Drug Invest 1987;2:23-30.

[27]. Fabrcgas J, Cucala C, Pous J. In vitro testing of an antacid formulation with prolonged gastric residence time. Drug DevInd Pharm 1994;20:1199-1212.

[28]. Chawla G, Gupta P, Koradia P, Bansal. A Gastroretention: A means to address regional variability in intestinal drug absorption. pharmaceutical technology 2003;27(2) 50-55.

[29]. Talukder R, Fissihi R. Gastroretentive delivery systems: A Mini review. Drug DevInd Pharm 2004; 30(10):1019-28.

[30]. Mojaverian P, Vlasses P, Kellner P. Rocci M. Effects of gender, posture, and age on gastric residence time of an indigestible solid: pharmaceutical considerations. Pharm Res 1988;10:639–64.

[31]. Whitehead L, Fell JT, Collett J. Development of a gastroretentive dosage form. Eur.

[32]. J.Pharmsci 1996;4(1):182-6.

[33]. Shivkumar H, Vishakante D. Floating controlled drug delivery systems for prolong gastric residence. Indian J Pharm Edu 2004;38(4):172-9.