World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

A COMPRESSIVE REVIEW ON FLOATING DRUG DELIVERY SYSTEM

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Article Received on 18/07/2022 **Article Revised on 08/08/2022** **Article Accepted on 28/08/2022**

ABSTRACT

The concept behind the development of Floating Drug Delivery System in certain drawback of conventional dosages form and to overcome the certain drawback related to physicochemical properties of drug molecule (API) and related the formulation development. Controlled/Sustained release floating drug delivery system is a suitable delivery system for a drug candidate having narrow absorption window sparingly soluble and insoluble drugs, drugs those locally release in stomach by oral administration shows degradability in colon or poor colonic absorption. Floating drug delivery system is a part of Gastroretentive drug delivery system that provides continuous controlled administration of less soluble drugs at the absorption site (Targeted site). In this review information related to floating drug delivery system with their advantages, disadvantages over the conventional drug delivery system. Which are helpful in development of dosages form under the condition of pharmaceutical aspects. Various types of techniques are development on the dosages form. Review focused on formulation aspect of effervescent floating drug delivery system, floating drug delivery system its types. The purpose of the review is to compile the work going on this delivery system, floating drug delivery system. The review provides the valuable information related to pharmaceutical formulation aspect to achieve gastric retention (prolong time) and discussed the various factors affect and to overcome it.

KEYWORDS: Floating drug delivery system, Types, Advantages, Disadvantages, factor affecting, pharmaceutical aspects.

INTRODUCTION

Oral delivery of drugs is the most preferable route of drug delivery due to its feature such as ease route of administration, low cost, patient compliance and flexibility in formulation etc. Oral sustained/controlled drug delivery formulations show some limitations connected with the gastric emptying time. The rapid gastrointestinal transit could result in uncomplete drug release from the device into the absorption window leading to decreases in efficacy of the administered dose. It is manifest from the recent research and patent literature survey that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists today.[1]

Gastric emptying of dosage forms (may be tablet, capsule or oral administered dosage form) is a variable process and ability to prolong and control emptying time is a valuable for dosage forms, which stay in the stomach for a longer period of time than normal dosage forms. One of the major drawbacks of floating drug dosage form is the ability to confine the dosage form in the desired area of the gastrointestinal tract.[2] To overcome on this physiological problem, several drug delivery systems with prolonged gastric retention time have been researched and investigated. Attempts are being made to develop a controlled drug delivery system that can show therapeutically effective plasma drug concentration levels for prolong time, thereby decreasing the dosing frequency and removing the fluctuations in plasma drug concentration at steady state by delivering drug in a controlled and reproducible manner (sustain release).[3]

Basic Anatomy and Physiology of Gastrointestinal Track

Basically, GIT is divided in three main region they are

1. Stomach
2. Small Intestine
3. Large Intestine

The internal structure of GIT consists of muscles tube. The size of muscles tube is about 9 meter which extends from mouth to anus. The main purpose of GIT is to store food, grind it, utilized its nutrients, and release slowly in duodenum and discard body waste material. The proper understanding of anatomy and physiology of stomach is

required for better development of Gastroretentive drug delivery system.[4]

Stomach contain approximately 50ml of liquid (Gastric fluid), which is known as HCL having pH 1-3, it is also called as stomach gastric fluid. The production of HCl is done by parietal cells (epithelium cell) of the stomach. The parietal cell is responsible for the control of gastric acid or gastric fluid. Whereas pepsinase is release by Zymogenic cell which are necessary for nutrient absorption.[5]

Anatomically structure of stomach is J shape is divided as Body, Fundus, Pylorus (Antrum) in three different layers of muscles. First layer of stomach is located at proximal part of stomach called oblique muscle; second layer located near the fundus which branches the third in higher region of stomach. The proximal tube consists of fundus and body which stores undigested material; while the pylorus work as elimination and it the location of mixing the motion which act as pump for gastric emptying by propelling action.[6]

Gastric Emptying Rate

Gastric emptying rate is systemic process regulated in defined phases; the normal gastric emptying rate is 1 to 4.5 Calories per minute. Gastric emptying is the regulated process consisting of different phases. Gastric emptying happens in both states such as fed state and fasting state, but the mobility pattern of stomach i.e., Migrating myoelectric complex (MMC) varies in both states. During fasting state an interdigestive series of electrical take place. This series is performed in cycle having 4 stages during 90 – 120 min this series is called as Migrating myoelectric complex. The cycle starts from lower esophagus and ended to ileum.[7,8]

Advantages of Floating Drug Delivery System[9]

Floating Drug Delivery dosage systems form an important technological drug delivery system includes tablets, capsules, pellets etc., with gastric retentive behavior and offer several advantages in drug delivery.
These advantages include:[10]

1. To improved drug absorption, because of increased in GRT and dosage form at its absorption site for prolong time
2. Controlled release delivery of drugs from the device.
3. Drug delivery shows local action in the stomach.
4. Reducing the mucosal irritation due to drugs, by drug releasing controlled drug.
5. Used in the treatment of GIT disorders such as gastroesophageal reflux.
6. Requires simple and conventional equipment for manufacture.
7. Ease route for administration and better patient compliance.
8. Site-specific drug delivery (Target drug delivery).

Disadvantages of Floating Drug Delivery System[11,12]

1. Gastric retention is affected by many factors such as gastric fluid concentration, gastric motility, pH and presence of food. But those factors are never constant and hence the buoyancy is not be predicted.
2. Drugs causing irritation to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
3. The swelling formulation can be swelled in the system before reaching the site of the stomach
4. Gastric emptying of floating dosage forms in supine subjects may occur randomly and becomes highly dependent on the diameter, shape and size. Hence floating dosage form should not be taken while going to bed.

Factors Affecting Gastro-retentive Time in Floating Drug Delivery System[13]

1. Particle Size: - particle size range from 1 – 2 micrometers (mm). which go to intestinal membrane.
2. Density: - The time or rate of gastric emptying is affected by the density of the dosage from.
3. Size of dosage from: - for extended GRT, the particle size of dosage form must be larger than 7.5 mm in diameter.
4. Shape of dosage form: - Dosage form shapes are responsible for the better GRT, which is 90 to 100%. The shaped involved are a tetrahedron, ring shaped devices compared to other shapes dosage from.
5. Nature of Food: - The nature of food affects the stomach motility pattern there are some factors that it is indigestible polymer.
6. Temperature of the food: - The temperature of the food reduced the gastric emptying rate.
7. Calories content of the food: - The calories food such as protein or fats are able to improve gastric retention time (4 to 10 hrs.)
8. Frequency of feeding: -A high amount of feeding is increased gastric retention time of the stomach (400 minutes).
9. Gender: -The gastric retention time in female is 4-6 hrs with their height, weight and body surface of the patients and in male is 3-4 hrs.
10. Age: - For people over 70, the GRT is much longer
11. Poster: -The patient's posture may change GRT.
12. Concomitant drug administration: - Antacids drug like Aluminium hydroxide, anticholinergic drug like atropine, narcotic analgesics and opiates like codeine may stimulate and prolong GRT.

Drug candidates Suitable for Floating Drug Delivery[14]

Drugs which targets site-specific absorption in the stomach or upper parts of the small intestine e.g. Furosemide, riboflavine-5- phosphate, drugs required for local therapeutic action in the stomach such as antacids, anti-H.Pylori agents, misoprostol, drugs unstable in the lower part of Gastro-intestinal tract such as captopril, drugs insoluble in intestinal fluids e.g., quinidine,

diazepam, drugs with variable bioavailability such as satolol.

Types of Floating Drug Delivery System

There has been a large development of oral control release and sustain release drug delivery system for gastrointestinal diseases, for prolong absorption of drug. This system improv the bioavailability in Gastroretentive track and maintain an effective drug concentration for prolong time in stomach (GIT).

As oral drug (Tablet, Capsule, Pellets) administered orally in stomach there is retention of drug in stomach and release drug in controlled manner. Due to controlled and sustained release the drug will supplied continuously to its absorption site or targeted site. It also a pH base drug delivery system i.e., drug release at the certain pH there is heavy coating of metal which prevent it dissolving from gastric fluid and dissolved at targeted site.

Current review deals with various Orally controlled release drug delivery system that have been recently become leading methodology in the field of site-specific drug delivery, controlled release drug delivery.[15]

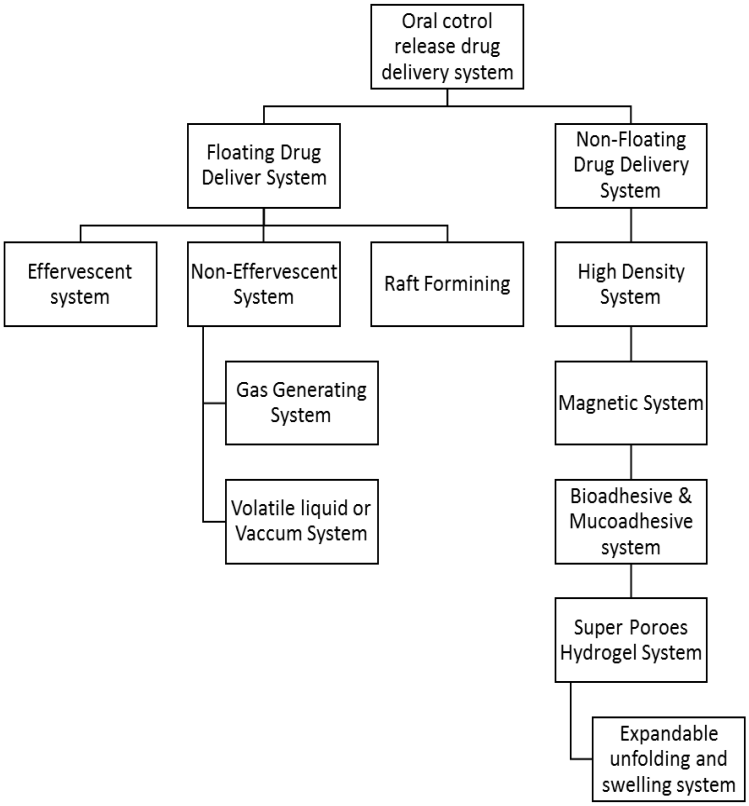

Figure 1: Types of floating drug delivery systems.

1. Floating Drug Delivery System[16]

Initially the floating drug delivery system was introduced by sir Davis in year 1968. In floating drug delivery system, the bulk density is lower than that of gastric fluid hence remain prolong time in stomach or targeted site, it releases it drug in control manner. The floating drug delivery does not affect the rate of gastric emptying over a prolong time.

The gastric emptying of residual system is followed by drug release in stomach. Thus, improve bioavailability and control over plasma drug concentration and increases its gastric retention time

Properties for FDDS

- Slow drug release
- Act as drug reservoir
- Bulk density should be lower than gastric fluid (Approximately 1.004 – 1.0 gm/cm).
- Must form a cohesive gel barrier

i) Effervescent System

The effervescent system matrix is prepared with swellable polymer such as Tartaric acid, HPMC, chitosan and effervescent compound like sodium bicarbonate, citric acid etc. Effervescent preparation may enhance the absorption and gastric pH in GIT. Bioavailability of effervescent tablet is more than the normal tablet.[12]

Effervescent dosage form (Tablet) containing sodium bicarbonate/ tartaric acid or citric acid when undergo reaction in stomach produce carbon dioxide i.e., development effervescent. The effervescent reduces the density of tablet dosage form and make it floatable on gastric fluid in stomach. For the production of

effervescent (carbon dioxide) sodium bicarbonate is treated with citric acid in the ratio of 0:76:1. In effervescent system drug are stored in reservoir, drug release in control or sustain manner when effervescent are produced in gastric fluid.[17]

(a) Gas Generating System

Gas generation system comes under the effervescent system. Hence this system also works on the effervescent reaction by reacting sodium bicarbonate and citric acid to liberate carbon dioxide. The drug entrapped in hydrocolloid layer decreases its specific gravity and density and make it float over gastric content after the releases of gases, gas generation or production of carbon dioxide(effervescent).[18]

(b) Gas Generating System

The volatile liquid and vacuum system are the recent approaches in gastro retentive drug delivery system. This system includes inflatable chamber filled with volatile oils such as ether, cyclopentane, which are gasified at body temperature. The drug releases after the volatile liquid releases. The inflatable chamber may also fill with a bio erodible polymer plug composed of poly vinyl alcohol, polyethylene etc.[19]

ii) Non – Effervescent System

In the preparation of non – effervescent system matrix forming polymer such as polymethacrylate, polyacrylate, polystyrene and highly swellable and gel forming substances such as polysaccharide and hydrocolloids are used. As non – effervescent drug (dosage form tablet, capsule, pellets) administered orally comes in contact with gastric fluid present in stomach pH ranges to 1 – 3 pH gets swell and become bulky losses its density less than 1. The gel formed structure of non – effervescent dosage form act as a reservoir and allow the content to release in control for prolong time. The best approaches of non – effervescent is porous present on the surface an osmatic condition is formed the dosage form swell large or several times more as compared to other oral dosage form when reacted with gastric fluid. Due to which the gastric concentration of stomach pushes the dosage form to pylorus but due to increase in size swelling the pressure through it back on the surface. Hence, dosage form float on the surface of gastric fluid with slow drug release and has a great absorption.[20]

iii) Raft Forming

The raft forming system is mainly used for the treatment of GERD – gastric esophageal reflux diseases. In raft forming system there is formation of viscous cohesive gel when comes in contact with gastric fluid. Due to which overall portion of the liquid gel swells and form a continuous layer called as raft, on the surface of gastric fluid.

Raft forming system includes carbonate / bicarbonate due to which dosage form become bulky and are responsible for liberating carbon dioxide to make system less dense. In raft forming system the gel forming agent are sodium alginate which converts in to raft after reacting with gastric fluid and also prevent reflux of gastric content in to the esophagus.[21]

2. Non – Floating Drug Delivery System

In non – floating drug delivery system the dosage form of gastro retentive drug delivery system does not float in the stomach but stays remain in the stomach by different mechanism. The drug may settle down in stomach showing bioadhesive and mucoadhesive properties, in this system dosage form release drug in sustain manner it also releases it drug at targeted site it is also pH dependent drug delivery system it gets dissolve at a certain pH.[9]

Further non – floating system are divided as

i) High Density System

When high density dosage form (capsule, Tablet, pellets) is given to patient by oral route of administration the dosage form settles down at the bottom or sink in stomach, by entrapped in antrum and withstand the peristaltic wave of the stomach wall. In high density drug delivery system formulation are formulated by coating layer of heavy metal or by mixing inert material with pharmaceutical preparation. The inert material may be zinc oxide, barium sulphate, oxides, titanium oxide etc., those inert material are mixed with pharmaceutical preparation (Dosage form) so that the density of the formulation exceeds the density of normal gastric content. The inert material increases the density up to 1.5 – 2.4 gm/cm3, according to the density present in the stomach GI transit time of pellet can be extent from 6 – 24 hours (as they are small in size), its rate of dispersion decreases. The product of high-density system is not marketed because its ineffective in humans till, research and development are ben working on it.[22]

ii) Magnetic System

In magnetic system approaches, a small magnet is inserted in dosage form as well as in abdomen over the position. The gastric residence time of dosage form can be enhanced by extra incorporated of magnet. Prolong absorption of drug is possible. Initially the technological experiment was performed on rabbit with bioadhesive granule containing ultra-fine ferrite. Granule where transfer to esophagus with an external magnet of 1700 G for the initial 2 min and (interval of 2 min) almost all the granules were retained in the region after 2 – 10 hrs.[16]

iii) Bioadhesive / Mucoadhesive System[23]

In bioadhesive drug delivery system there is used of lumen as a drug delivery device to enhance the drug absorption on the targeted site. In this system there is use of adhesive polymer which adhere on epithelial surface of stomach and gives prolong absorption of drug.

As compared to bioadhesive mucoadhesive is not so strong adhesive due to frequently release of mucous by

gastric mucous. To overcome on those defect dilution of stomach content (gastric fluid) is necessary.

To have a complete adhere in mucosal membrane some excipients are used such as lectins, Carbopol, chitosan, glidin etc., those excipients help to increases absorption for prolong time in stomach as well as GI track. This system is also based on target drug delivery, site specific delivery.

iv) Super pores Hydrogel System

The super pores hydrogel system contains interconnected microscopic pores those pores are responsible for absorption of water in short period of time, the water absorption capacity should be high due to limitation of time. The super pores hydrogel system is the interconnected network of hydrophilic polymer and due to presence of super-size pores capillary action occurs and swelling o dosage form is observed. In the preparation of super pores hydrogel system ingredients such as crosslinker, stabilizer, foaming aid, foaming agent are added with diluent water. Super pore hydrogel system has fast swelling as well as high swelling capacity, stability in acidic condition of stomach, high mechanical strength. The average pore size of 100 micrometer is used to improve gastro retention time.[24]

v) Expandable unfolding and swelling system[25]

In this drug delivery approaches the dosage size increases as dosage form reacted to gastric fluid. The size of dosage form (tablet, capsule, pellets) gets bigger than the pyloric sphincter. The swelling is due to presence of swelling expandable agent such as gel, cellulose, HPMC etc., are responsible for swelling through osmatic absorption of water or gastric fluid. Initially the dosage form should be in normal condition as the dosage form is ingested through oral route of administration the reaction occur in stomach the dosage form get swell and float on the surface.

Expendable unfoldable and swelling system are recently investigated and developed and are observed effective GRDDS. In unfoldable system generally there is use of biodegradable polymer due to its presence in different size dimension which gets easily compressed within capsule and extend in stomach by osmatic absorption of water.

This system has also reported some disadvantage such as easy storage of hydro sable, biodegradable, etc., short mechanical shape. In unfolding system, it is difficult to industrialize because it is cost effective, drug delivery may cause brief obstruction, intestinal adhesive and gastropathy.

Following points are essential for the development of expendable system: -

- It should be in small (normal) dosage form for oral intake.
- Expanded Gastroretentive form
- Should not cause gastric destruction
- Finally, it should become small after releasing drug content from system.

Pharmaceutical Aspects[14]

While designing the floating drug delivery system following condition should be mention: -

1. Drug (Dosage form) retention in the stomach according to the clinical demand.
2. Oral administration of dosage form.
3. Should able to load substantial amount of drug according to physicochemical properties and release them in a controlled/sustained manner.
4. There should be complete matrix integrity of the sustain release formulation in the stomach, the expensive in industrial manufacture should be minimum, the drug should optimization between the buoyancy time and release rate, lag time i.e., the time taken by the dosage form to float. Most of the floating systems are found to be single unit system; the single unit systems are unreliable and irreproducible for prolong time in the stomach when orally administered. On the other hand, multiple-unit dosage system is the better form because it reduces the interfacial tension and lower the absorption and dose dumping.

CONCLUSION

From the survey of various literature, drug absorption in the gastrointestinal tract is a highly variable procedure with different physiochemical properties. FDDS has prolong gastric retention of the dosage form extends the time for drug absorption. The purpose of Gastro-retentive floating drug delivery systems is to enhancing the bioavailability and controlled drug delivery of many drugs. The floating drug delivery system provide a potential approach for gastric retention, increases gastric retentive drug delivery to optimize the delivery of molecules. This review gives an over view on pharmaceutical parameters, pharmaceutical dosage form, factor affecting gastric emptying etc.

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