International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 2406-2412 www.ijprajournal.com ISSN: 2249-7781

Floating Beads

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Submitted: 25-02-2023 Accepted: 06-03-2023

ABSTRACT

The main aim of any drug delivery system is to bring about the desired concentration of the drug in blood or tissue, which is therapeutically effective and nontoxic for a prolonged period. The recent developments of FDDS are including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple-unit floating systems. Floating beads are used for controlled drug release as they have gastro retentive property without affecting the gastric emptying rate. Gastro retentive delivery systems can be retained in the stomach and assist in enhancing absorption and the bioavailability of drug which has a narrow absorption window in a particular region of gastrointestinal tract. This can be achieved by using various natural polymers.

Keywords: Floating dosage form, floating beads, method of preparation, and evaluation of beads.

I. INTRODUCTION

The majority of therapeutic applications continue to favour oral drug delivery due to its evident benefits, such as convenience of administration, patient compliance, and formulation flexibility.1 There have been many oral controlled drug delivery systems investigated that release the medicine at a predetermined, predictable pace and also optimise the therapeutic effect by managing the release of the drug.2 This method is, however, hindered by a number of physiological issues, such as the inability to contain and localise the drug delivery system within the appropriate region of the gastrointestinal tract (GIT) due to fluctuating stomach emptying and motility.3 People normally have a gastric emptying time of 2-3 hours through the primary absorption area, which might cause an incomplete drug release from a controlled drug delivery system and reduce the effectiveness of a dose that is provided.4 For drugs functioning locally in the GIT, the capacity of a dose form to extend and regulate the stomach emptying time is an important advantage [5]. These factors resulted in the development of gastroretentive dosage forms, which have the ability to maintain stomach retention for extended periods of time, reducing the frequency of drug dosing [4]. One of the most useful methods for obtaining a prolonged and predictable drug delivery profile in the GIT is the use of gastroretentive dosage forms. 6 These are made to stay in the stomach for a longer period of time in order to increase the residence time of dosage forms, which enhances the drug's bioavailability [7,8]. They enable oral therapy for medications with a constrained upper GIT absorption window or poor colon stability. The medication can also exert local effects within the stomach, and continuous close contact with the absorbing membrane boosts its effectiveness [9]. Also, these dose forms are particularly suitable for medications with low pH solubility [10]. Several dose formulations have been developed during the past few decades to extend the drug's gastric residence time (GRT). These include of muco/bioadhesive systems, floating systems, expandable systems, superporous hydrogel systems, magnetic systems, and high density systems. The most practical, cost-effective, and process takes among the various options is gastric floating medication delivery devices [11]. Utilizing all of the pharmacokinetic and pharmacodynamic benefits of controlled release dosage forms is made possible by include the drug in the floating dosage form [12]. The formulation of floating drug delivery systems (FDDS) can make use of a variety of excipients with natural or synthetic sources. Granules, powders, capsules, tablets, laminated films, hollow microspheres, and other substances have all been studied as possible floating dosage forms [7].

DEFINITION

Floating systems are low – density system that have sufficient resistance to float on the

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stomach and stay float in gastric without creating any effect on the gastric emptying rate for a long period of time. While the system floats on the gastric contents the drug will be released slowly at the desire concentration in the system.Thus, the residue will be cleared from the stomach. Then these results will conduct to GRT elevation and be better control of flux in plasma drug concentrations. It also useful for proximal gastrointestinal tracts local drugs for example antibiotics for Helicobacter pylori on the manage for a peptic ulcer and for drugs that difficult to dissolve or not stable in intestinal fluids [3].

1. Anatomy & Physiology of Stomach

Fundus, Body, and Pylorus are the three anatomical regions of the stomach (or antrum) [15]. The distal part (pylorus) is the main site of mixing motions, working as a pump to propel gastric content for gastric emptying, while the proximal region (Fundus and body) serves as a reservoir for ingested materials. Both when one is eaten and when one is fasting, the stomach empties. Every 2 to 3 hours when someone is fasting, an interdigestive series of electrical events cycle through the stomach and small intestine. The activity and transit of dosage forms are controlled by the migrating myoelectric complex (MMC), also known as the interdigestive myoelectric cycle. It is characterized by four Phases:

1. Phase I (basal phase)
2. Phase II (pre burst phase)
3. Phase III (burst phase)
4. Phase IV.

Phase I

In this phase the gastric emptying rate is slow as the onset of MMC is delayed. this phase usually lasts for 30 to 60 min. Contraction does not occur in this phase. it is also known as basal phase.

Phase II

In this phase bile secretion and mucus discharge take place and intermediate contraction occurs. It lasts for 20- 40 mins. It is also known as pre- burst phase. The intensity and frequency increase gradually as the phase progresses.

Phase III

In this phase, regular and intense contraction take place for a short time. It last usually for 10-20 min. this phase also called as housekeeper wave as it tends to empty the fasting contents of the stomach. Large objective remains in the stomach in the stomach in the fed state but passed down to the intestine during this phase.

Phase IV

Last for 0 -5 minutes and occur between phase III and I of 2 consecutive cycle. After ingesting a mixed meal, the contraction pattern changes from a fast to a fed condition. This also known as digestive motility pattern and comprises continuous contraction as in phase II of fasted state. The fed state experiences a delayed onset of MMC, which slows the rate at which the stomach empties[4].

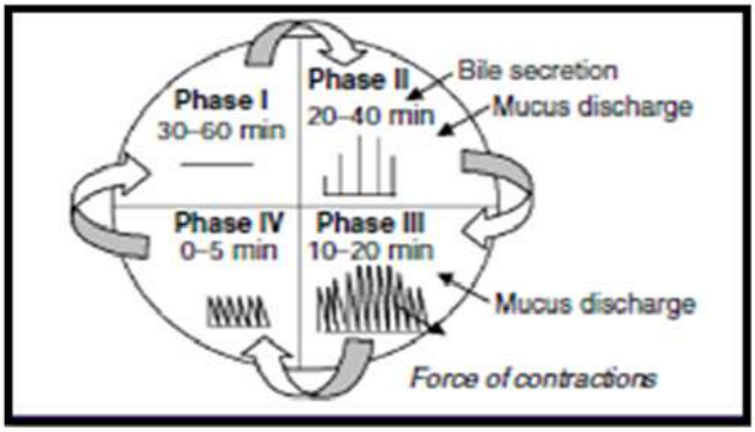

Figure1: Gastric motility pattern

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Need for gastric retention

 Drugs that are absorbed from the proximal a part of the canal (GIT). Drugs that are less soluble or are degraded by the alkaline pH they encounter at the lower a part of GIT.

 Drugs that are absorbed due to variable internal organ evacuation time. Local or sustained drug delivery to the abdomen and proximal bowel to treat bound conditions.

 Mostly very useful for the treatment of peptic ulcers caused by Helicobacter pylori infections [1].

2. APPROACHES OF STOMACH RETENTION

Various approaches are pursed to extended the retention of Associate in Nursing oral dose type within the abdomen for instance, bioadhesive approach during which the adhesive capability of some chemical compounds with conjugated protein is closely applied to the animal tissue surface of abdomen.

1. High density approach

For making ready such variety of formulation, the density of the pellets ought to be over the abdomen fluid. It might be a minimum of one 50 G / ml during this kind the drug will be coated or mixed with significant, nontoxic material like sulfate oxide, etc.

2. Low density approach: floating systems come back

Below tenuity approach during this approach, the density of pellets ought to be but one g/ ml thus on float the pellets or tablets within the internal organ fluid and unleash the drug slowly for a extended amount of your time.

3. ADVANTAGES OF FDDS

1. Floating dosage form such as tablets or capsules will remains in the solution for prolonged time event alkaline pH of the intestine.
2. FDDS are advantages for drugs meant for local action in the stomach e:g Antacids .
3. FDDS dosage forms are advantage in case of vigorous intestinal movement and in diarrhoea to keep the drug in floating condition in stomach to get a relatively better response.
4. Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence FDDS formulation may be useful for the administration of aspirin and other similar drugs.
5. The FDDS are advantages for drugs absorbed through the stomach e:g ferrous salts .
6. Slow release of the drug into the body minimize the counter activity leading to higher drug efficacy.
7. FDDS reduce the drug concentration fluctuation over a critical concentration and thus enhance the pharmacological effects and improves the clinical outcomes.
8. A floating dosage form is a widely accepted approach especially for drugs which have limited absorption site in upper small intestine [12].

4. DISADVANTAGES OF FDDS

1. This system required a high level of fluid in the stomach for drugdeliveryto float and work efficient coat.Not suitable for drugs that have solubility or stability problem in GIT.
2. Drugs such as Nifedipine (calcium channel blocker) which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
3. Drugs which are irritated to gastric mucosa are also not desirable or suitable.
4. The drug substance that are unstable in the acidic environment of the stomach are not suitable.
5. The dosage form should be administrated with a full glass of water.
6. The dosage form should be administered with a full glass of water (200- 250 ml)
7. Primarily absorbed from stomach and upper part of GI tract e.g calcium supplement, chlordiazepoxide and cinnarizine [13].

5. Mechanism of floating drug delivery system [20,8]

Low density floating medication delivery systems that have enough buoyancy to float above gastric contents and stay in the stomach for a long time are called floating drug delivery systems. The medicine is released slowly and at the desired rate when the system floats over the contents of the stomach, increasing gastro-retention time and reducing fluctuation.However, in addition to the minimal gastric content necessary for the successful application of the buoyancy retention principle, the dosage form also needs to have a minimal amount of floating force (F) to remain buoyant on the surface. The device operates by continually measuring the force in units of F as a function of time needed to keep the submerged objects. The object floats better if F is on the higher positive side as shown in figure [4]. This device aids in FDDS optimization with regard to the stability and longevity of the floating forces generated in order to avoid the negative effects of unforeseen intra gastric buoyancy capability

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fluctuations. F = F buoyancy – F gravity F = (DF – Ds) gv- - - (1) Where, F= total vertical force, DF = fluid density, Ds= object density, g = acceleration due to gravity v = volume and

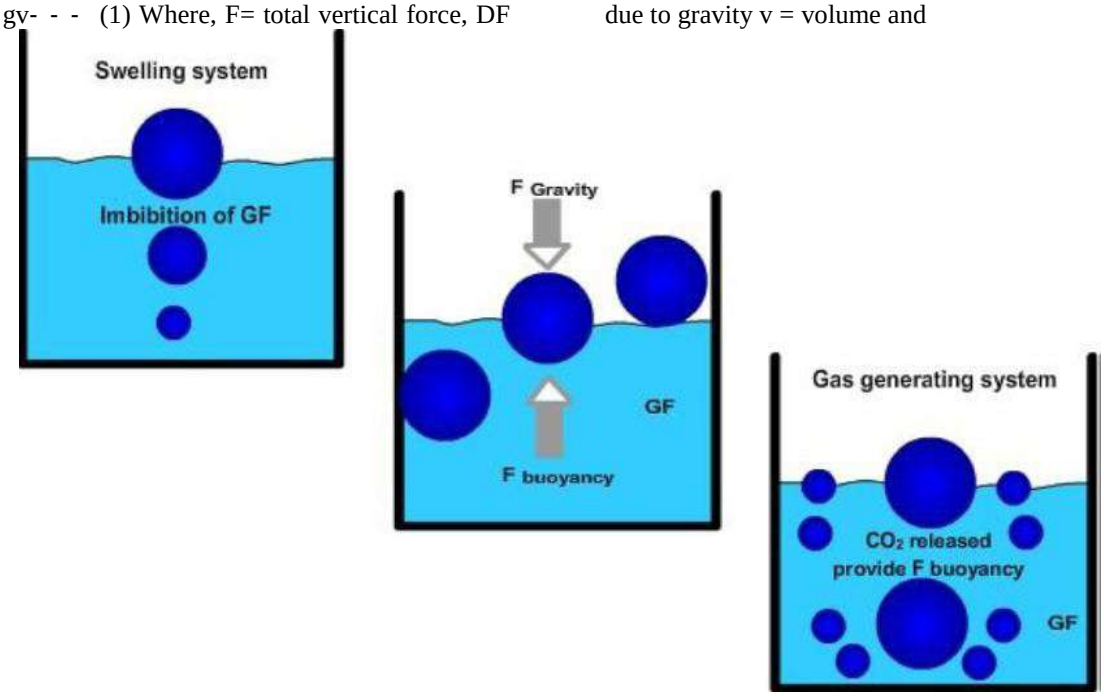

Figure 4: Mechanism of Floating System, GF= Gastric Fluid

6. **Gastroretentive floating beads: [2]** Micro beads are tiny, solid, free-flowing particle carriers that include a coating or core that contains a medication. Beads can provide controlled / sustained release properties and as such bioavailability of drugs are enhanced. Gastro retentive beads are not just to sustain the drug release, but also to enhance gastric residence of the dosage forms until the entire drugs are completely released at the desired period of time. The multiparticulate dosage forms have many advantages as compared to single unit preparations, such as:

 Greater flexibility
 Avoid dose dumping and incomplete drug release
 Reduction of inter- and intra-subject variability in drug absorption
 Increase bioavailability
 Increase flow property

7.1 Commonly Employed Polymers in Gastro retentive Floating Beads:

 Sodium Alginate:

Sodium alginate is a naturally occurring polysaccharide and an anionic linear polymer having chains that are arbitrarily organised with residues of 1, 4-linked L-glucuronic acid and 1, 4-linked D-mannuronic acid. It is a stable gel that contains Ca2+, a divalent cation used in the prolonged release of medications. Alginate has high mucoadhesive properties, is biodegradable, and has mild gelation conditions. Alginate beads' stability in acidic media makes them useful for floating drug delivery since they stop drugs from degrading in the stomach's acidic environment [11,12].

 Pectin:

Pectin is a colloidal polygalacturonic acid where some of the carboxylic groups are esterified with methyl groups. D-galectouronic acid is the main constituent of pectin. It is a low methoxy polysaccharide polymer, with a degree of esterification is < 50 %. It can form gels in the presence of calcium ions or other multivalent cations. Pectin minimises the interfacial tension between oil and water phase and used for the preparation of emulsions. The USP 28 reports, pectin as a purified carbohydrate product which is obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace [13,14].

 Chitosan:

Chitosan is a useful excipient for preparing sustained release formulation and for increasing the bioavailability of poorly water-soluble drug. Chitosan obtained by alkaline

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deacetylation of Chitin, which is a non-toxic, biocompatible, and biodegradable natural polymer. Chitosan-based hydrogel polymeric beads were studied as Nano or micro -particulate carriers in the pharmaceutical and medical fields [5,15]. During the incubation, the presence of calcium ions in the chitosan solution having a great effect on the ability of a gel bead to bind chitosan. As increase in the concentration of calcium chloride, there will be an increase in the rate and extent of chitosan binding process [18].

Guar Gum:

A galactomannan called guar gum is made from the Cyamopsis tetragonolobus plant. It is a polysaccharide made up of galactose and mannose repeating units. A linear chain of 1,4-linked mannose residues makes up the backbone, and every other mannose, 1,6-linked galactose residues create small side branches. Guar gum is temperature and acidic pH (range 5-7) stable. Guar gum hydrolyzes and loses viscosity at temperatures above 500°C and in strong acids with a pH of three or less. Guar gum is a superior emulsifier than locust bean gum because it has more galactose branch points and is more soluble [16,17].

7.2 Floating beads can be prepared by:[2,19]

Emulsion Gelation Method:

In this method the polymer is dissolved in distilled water which is kept in a magnetic stirrer. After complete homogenization of polymer required quantity of oil is introduced then followed by drug. The resultant homogenous mixture containing drug, oil and polymer is introduced into 5% calcium chloride through 21G needle, which is left at room temperature. After specific period time the filter the solution, the resultant beads were washed twice through distilled water and dried at room temperature for 12 hrs.

Ionotropic gelation method:

The hydrogel beads are prepared by introducing a drug-loaded polymeric solution into the aqueous solution of polyvalent cations through the 21G needle. The cations tend to diffuse into the drug-loaded polymeric drops, resulting in the formation of a three dimensional lattice of ionically crosslinked moiety. These beads are then dropped in aqueous solution of 1% glutaraldehyde for about 1h. Under mild conditions, biomolecules can also be inserted into these gelispheres to maintain their three-dimensional structure. Beads are dried in an air convection type oven at 40°C for 6 h and in freeze dryer to evaluate the changes in beads.

7. Application of FDDS

Floating drug delivery offer many application for medication having poor bioavailability owing to the narrow absorption window within the higher apart of the epithelial duct. It retain the indefinite quantity type at the location of absorption and so enhances the bioavailability. These are summarized as:

1. Sustained drug delivery

The generally downside of short stomachic duration encountered with associated the atomic number 24 formulation thence are often overcome with these systems. HBS systems will stay within the abdomen for long amounts and then will unleash the drug over a chronic period of your time. These systems have a system are comparatively giant in size and spending from the opening gap is prohibited E.g sustained unleash floating capsules of nicardipine coordination compound were developed and were evaluated invivo [15].

2. Site specific Drug Delivery

These systems are notably advantageous for medication that are specifically absorbed from abdomen or the proximal a part of the tiny viscus Eg diuretic drug and vitamin B2. E.g
diuretic drug is primarily adsorbed from the abdomen followed by the small intestine. Its been rumoured that a monolithic floating indefinite quantity type with prolonged stomachic duration was developed and also the bioavailability was enhanced. AUC obtained with the floating indefinite quantity was about one 8 times those of typical diuretic drug indefinite quantity form [16].

3. Absorption Enhancement

Drugs that have poor bioavailability as a result of site specific absorption from the higher a part of the channel area unit potential candidates to be developed as floating drug delivery systems. There by rising their absorption E.g A significantly increase within the bioavailability of floating dose forms can be achieved as compared with commercially on the market dose type [17].

4. Maintenance of constant blood level

These systems give a straight forward manner of maintaining constant blood level with

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Associate in Nursing simple administration and higher patient compliance [18].

8. FACTOR AFFECTING GASTRIC RETENTION

Factor affecting gastric emptying. The mostvital parameters touching stomachal remotion
and hence, the stomachal retention time of oral indefinite quantity forms include:
1. Density: GRT may be operated of indefinite quantity kind buoyancy that's obsessed with the density.
2. Size: indefinite quantity kind units with a diameter of quite seven. 5mm or reportable to possess Associate in Nursing exaggerated GRT compared those with diameter of nine .9 mm
3. Single and multiple unit formulation: Multiple unit formulations show a lot of inevitable unharness profile and insignificant impairing of performance thanks to failure of units, permit co administration of units with totally different unharness profiles.
4. Fed or unfed state: Under fast conditions the GI motility is characterised by periods of study motor active or the migrating myoelectric advanced (MMC) that happens each 1.5 to 2 hours.
5. Nature of meal: Feeding of inedible polymer or carboxylic acid salts will modification the motility pattern of the abdomen to a fed state decreasing the stomach remotion rate and prolonging drug release
6. Calories content: GRT is exaggerated by four to ten hours with a meal that's high in protein and fats.
7. Frequency of feed: The GRT will increase by over 400 minutes once sequent meals are given.
8. Gender: Mean mobile GRT in male (3.4 ± 0.6 hour) is a smaller amount compared with their age and race matched feminine counterpart (4.6 ± 1.2 Hours)

9. Evaluation parameters of floating beads:[20,2,19]

Percentage yield:

Prepared floating beads were collected and weighed. Yield can be calculated by the following formula-
Weight of the prepared beads /Total weight of the drug and excipients

Drug Content and Drug Entrapment Efficiency:

Equivalent weight drug loaded polymer beads will be dissolved in suitable solvent. It will be stirred using magnetic stirrer. The resulting solution will be filtered and filtrate will be suitably diluted with suitable solvent. It can have determined spectrophotometrically. Drug content and Entrapment efficiency can be determined using equation:
Drug content = concentration x dilution factor /1000*100
Entrapment efficiency = Actual yield /Theoretical yield*100

In-vitro release studies for floating beads:

The in-vitro dissolution studies were carried out using USP Dissolution Apparatus type II at specific rpm. The dissolution medium contains of 0.1 N HCl (900 ml) maintained at 37±0.50C. Periodically 5ml sample were withdrawn at specific time interval and replaced with fresh medium to maintain the sink condition. Drug content was determined spectrophotometrically. % CDR is calculated by the calculation.

In vitro buoyancy study:

Required amount of beads were spread over the surface of a USP dissolution apparatus type II, consisting 900 ml of 0.1 N HCl and 0.02% Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 hr. The floating and the settled portions of beads were taken separately. The beads were dried and weighed. Buoyancy percentage was calculated as the ratio of the total mass of beads that remained floating and the total mass of the beads settled.
% buoyancy = Qf Qf + Qs Where, Qf = Weight of the floating Beads Qs = Weight of settled Beads

Scanning electron microscopy (SEM):

Morphological evaluation of the surface and internal structure of the prepared dried beads can be performed by using a scanning electron microscope (SEM).

Stability studies

The formulated beads were sealed in vials and kept for 90 days at 400C/75% RH. After 90 days of exposure the beads were studied for drug content determination and in-vitro release.

Acknowledgement-

I consider myself fortunate enough to be in the right place with a person. I take this opportunity to express my deep sense of gratitude and hearty thanks to Mr Sanjay Jain Sir for their valuable guidance, kind suggestion, and constant encouragement.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 2406-2412 www.ijprajournal.com ISSN: 2249-7781

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