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GASTRO RETENTIVE FLOATING BEADS – A NEW TREND OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT

The main object of any drug delivery system is to bring about the desire concentration of the drug in blood or tissue, which is therapeutically effective and non-toxic for a prolong period. The recent research and developement of FDDS(Float drug delivery system) affect gastric retention, approaches to design single unit and multiple unit floating systems. Floating beads are used for controlled drug release as they have gastroretentive properties without affecting the gastric emptying rate. This can be achieved by using natural polymers.

KEYWORDS: *Introduction, advantages, disadvantages, mechanism of floating drug delivery system, types, preparation, evaluation, application.*

INTRODUCTION

Gastroretentive drug delivery system(GRDDS) is a novel drug delivery system which has over merits to conventional drug delivery system owning to its prolonged retention ability in the stomach and thereby increase bioavailability of drug.[1-4]

Gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach, low density (floating) systems that float in gastric fluid, mucoadhesive systems that cause bioadhesion stomach mucosa, unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincture of stomach, superporous hydrogel systems, magnetic systems etc. The current review deals with floating type gastroretentive drug delivery system. Floating microspheres are promises to be a potential approach: This system also provide opportunities in the designing of new controlled and delayed release oral formulations.[5,6]

Drug candidate suitable for gastroretentive drug delivery system

1) Drugs those are unstable in the intestinal or colonic environment
   e.g. metronidazole, ranitidine, captopril.
2) Drugs that have narrow absorption window in gastrointestinal tract (GIT)
   e.g. furosemide, paraaminobenzoic acid (PABA) riboflavin, L-DOPA.[7]
3) Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori.
4) Drugs those are locally active in the stomach e.g. antacids, misoprostol.
5) Drugs that exhibit low solubility at high pH values e.g. verapamil hydrochloride, diazepam, chlordiazepoxide.[8]

Drug candidate unsuitable for gastroretentive drug delivery systems

1) Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
2) Drugs that have very limited acid solubility e.g. phenytoin etc.
3) Drugs intended for selective release in the colon e.g. corticosteroids and 5 – amino salicylic acid etc.[9]

Advantages[10-15]

1. Enhanced bioavailability.
2. Enhanced first-pass biotransformation.
3. Sustained drug delivery/reduced frequency of dosing.
4. Targeted therapy for local ailments in the upper GIT.
5. Reduced fluctuations of drug concentration.
6. Minimization of fluctuations in drug concentration.
7. Reduced counter-activity of the body.
8. Extended time over critical (effective) concentration and Minimized adverse activity at the colon.
9. Site specific drug delivery and Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide.
10. Maintenance of constant therapeutic levels over a prolonged period.
11. The controlled, slow delivery of drug form gastro retentive dosage form provides sufficient local

action at the diseased site, thus minimizing or eliminating systemic exposure of drugs.
12. Gastro retentive dosage forms minimize the fluctuation of drug concentrations and effects. This feature is of special importance for drug with a narrow therapeutic index.
13. Minimize the counter activity of the body leading to higher drug efficiency4.

Disadvantages[16-20]

1. Unsuitable for drugs with limited acid solubility. E.g. Phenytoin
2. Unsuitable for drugs that is unstable in acidic environment. E.g. Erythromycin
3. Drugs that irritates or causes gastric lesions on slow release. E.g. Aspirin and NSAID's
4. Drugs that absorb selectively in colon. E.g. Corticosteroid
5. Drugs that absorb equally well through GIT. E.g. Isosorbide dinitrate, Nifidipine
6. Floating drug delivery systems require high fluid level in stomach to float.
7. Some drugs present in the floating system causes irritation to gastric mucosa.

Mechanism of floating drug delivery system

Floating drug delivery systems are low density systems than the gastric contents, which have adequate buoyancy to float over the gastric contents and continue to exist in the stomach for a prolonged period. When the system floats over the gastric contents, the drug is released slowly at the desired rate, results in enhanced gastro-retention time and minimize the fluctuation.[21]

However, a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimum level of floating force (F) is also required to keep the dosage form buoyant on the Surface. The apparatus works by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if F is on the higher positive side as shown in fig. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.[22,23]

F = F buoyancy – F gravity

F = (DF – Ds) gv

Where, F= total vertical force,

DF = fluid density,

Ds= object density,

v = volume and

g = acceleration due to gravity.

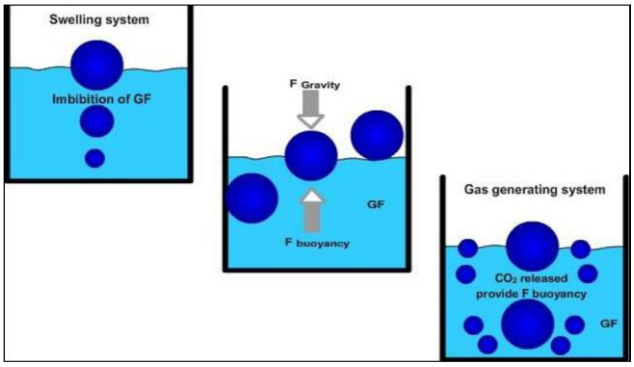

Figure 1: Mechanism of floating drug delivery system.

Foating drug delivary system categories into effervescent and non-effervescent system.

Effervescent system

It is a matrix type of system prepared with the aid of swellable polymer example-methylcellulose and chitosan and other effervescent compound such as : sodium bicarbonate, tartaric acid, citric acid etc. Such compounds comes in contact with gastric content, CO_2 is liberated and gets entrapped in swollen hudrocolloid which provide it float over a time.[24]

Again classified into

1) Gas generating system- These system utilize effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid. CO2 is released in this system result the formulation to float in the stomach.Other material has been reported like mixture of sodium alginate and sodium bicarbonate, when ingested multiple unit floating pills that liberate carbondioxide.[25]

2) Volatile liquis containing system- The GRT of the drug delivery systemcan be sustained by incorporating an inflammable chamber which contain a liquid, e.g, ether , cyclopantane, at body temperature it gastifies.[26]

Non-effervescent system

It is used as a gel formimg or swellable cellulose type of hydrocolloids. After oral administration, the drug with gel forming hydrocolloids swell in contect with gastric fluid and maintain integrity of the shape and bulk density barrier, by the swollen polymer the air trapped result in the buoyancy in the dosage form.

Classifiesd into

Colloidal gel barrtier system

System containing drug with gel forming hydrocolloids which remain buoyant on the stomach contents. This increases GI resistance time and enhances drug reaching to absorption site in the solution form which is ready for absorption. In this system contact with gastric fluid, the hydrochlorides hydrates and form a colloidal gel barrier around its surface. The formed colloidal gel barrier controls the rate of fluid penetration into the device and followed by release of the drug.[27]

Microporous compartment system

This system is based on the encapsulation of a drug reservoir inside a microporous compartment eith aperture along its top and bottom walls. The drug reservoir present in compartment and its peripheral wall is completely sealed to prevent direct contact of gastric mucasal surface with the undissolved drug. Air entrapped in the stomach in the floatation chamber causing the drug delivery to float over the gastric content. Gastric fluid enters through the pores, dissolved the drug and carrier, the dissolved drug for continuous transport across the intestine for absorption.[28]

Alginate beads

By dropping sodium alginate solution into calcium chloride aqueous solution , a spherical beads approx. 2.5mm in diameter can be prepared ,and then separated,snap-frozen in liquid nitrogen, and freeze dried at -40degree C for 24hours, resulting in a porous system formed which can float over 12hours.[29]

Hollow microsphere

It is carried with drug in their outer polymer shelf, which is prepared by a novel emulsion solvent diffusion method.

Floating beads can be prepared by
Emulsioin Gelation method

In this method the polymer dissolved in dist. 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 homogenization mixture containing drug, oil and polymer is introduced into 5% CaCl2 through 21G needle, which is kept in room temp. After sfecific period of time filter the solution, the resultant beads were washed twice through dist. water and droed at room temp for 12 hrs.[15]

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, result in the formation of 3D lattice of ionically cross-linked moiety. The beads are then dropped in aq. Solution of gluteraldehydefor 1hr.[17]

Factors affecting gastric retention time of the preparation

1) Density-should be lower than that of the gastric fluidal contents (1.004 g/ml)
2) Size-the diameter of more than 7.5 mm.
3) Incidence of feeding-GRT can rise by more than 400 min when consecutive
4) foods are dispense compared to a single meal due to low-frequency MMC.
5) Caloric content can be increased by 4-10 with foods high in protein and fat.

Evaluation gastro retentive floating drug delivery systems

1) Percentage yield

$$\frac{\text{Weight of dry material obtained}}{\text{Total weight of raw material}} * 100$$

2) Swelling index

This is calculated from,

$$\frac{\text{Weight of wet material – Weight of dry material}}{\text{Weight of wet material}} * 100$$

3) Drug entrapment efficiency

The capture efficiency of the multiparticulate or the percent entrapment can be determined by allowing washed multiparticulate to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency is calculated using equation.[21]

4) Particle size analysis

The particle size and the size distribution of beads or microspheres is determined in the dry state using the optical microscopy method.

5) Surface characterization

The external and cross-sectional morphology (surface characterization) is done by scanning electron microscope (SEM).

6) Floating lag time

It is the time taken by the tablet to emerge onto the surface of dissolution medium and is expressed in seconds or minutes.

7) Buoyancy time

Appropriate quantity of the floating micro particulate is placed in 100 ml of the simulated gastric fluid (SGF, pH 2.0), the mixture is stirred with a magnetic stirrer. The layer of buoyant micro particulate is pipette and separated by filtration. Particles in the sinking particulate layer are separated by filtration. Particles of both types are dried in a desiccators until constant weight is achieved. Both the fractions of microspheres are weighed and buoyancy is determined by the weight ratio of floating particles to the sum of floating and sinking particles.[25]

$$\text{Buoyancy time}(\%) = Wf / Wf + Ws \times 100$$

Where, Wf = Weight of floating
Ws = Weight of settled

8) Drug – Excipient interactions

This is done using FTIR. Appearance of a new peak, and/or disappearance of original drug or excipient peak indicates the DE interaction.

9) In Vitro drug release

This is determined by using USP II apparatus (paddle) stirring at a speed of 50 or 100 rpm at 37±0.2 °c in simulated gastric fluid (pH 1.2 without pepsin). Aliquots of the samples are collected and analysed for the drug content. The time (hrs) for which the tablets remain buoyant on the surface of the dissolution medium is the duration of floating and is visually observed.[19]

10) In Vivo evaluation:

This is carried out by means of X-ray or Gamma scintigraphic monitoring of the dosage form transition in the GIT. The tablets are also evaluated for hardness, weight variation, etc.

Applications

1) Site- Specific drug delivery

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., Riboflavin, furosemide. Bilayer-floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin E1 used as a protectant of gastric ulcers caused by administration of NSAIDs.[27]

2) Absorption enhancement

Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

3) Sustained drug delivery

Hollow microspheres of non-steroidal anti inflammatory drugs are very effective for controlled release as well as it reduces the major side effect of gastric irritation; for eg. floating microspheres of indomethacin are quiet beneficial for rheumatic patients.[24]

4) Floating system are particularly useful for acid stable drugs, drugs which are poorly soluble or unstable in intestinal fluids and for those which undergo abrupt changes in their pH-dependent solubility due to food, age and pathophysiological conditions of GIT. e.g. floating system for furosemide lead to potential treatment of Parkinson's disease.

5) The floating dosage form by virtue of its floating ability was retained in stomach and maintained high concentration of drug in the stomach.

6) There are some cases in which the relative bioavailability of floating dosage form is reduced as compared to conventional dosage form e.g. floating tablets of amoxicillin trihydrate has bioavailability reduced to 80.5% when compared with conventional capsules.

Table Marketed products of GFDDS.[28,29]

Sr. No.	Brand name	Drug (Dose)	Company , Country	Remarks
1.	Modopar	Levodopa (100 mg) Benserazide (25 mg)	Roche Product USA	Floating CR capsule
2.	Valrelease	Diazepam (15 mg)	Hoffmann – LaRoche USA	Floating capsule
3.	Topalkan	Al-Mg antacid	Pierre Fabre Drug France	Floating liquid alginate preparation
4.	Conviron	Ferrous sulphate	Ranbaxy India	Colloidal gel forming FDDS
5.	Cifran OD	Ciprofloxacin (1 gm)	Ranbaxy India	Gas generating floating tablet
6.	Cytotec	Misoprostal (100 mcg/200 mcg)	Pharmacia USA	Bilayer floating capsule
7.	Oflin OD	Ofloxacin (400 mg)	Ranbaxy India	Gas generating floating tablet
8.	Liquid Gavison	Al hydroxide (95 mg) Mg carbonate (358 mg)	Glaxo Smith Kine India	Effervescent floating liquid alginate preparation

CONCLUSION

Gastro retentive drug delivery systems offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. One of the main applications of gastric retention drug delivery system on treatment of *H. pylori* infection is promising area of research in pharmaceutical industry and academia. Based on literature, we concluded that gastric retention drug delivery system has more scope to file patent and lot of opportunity available to market the product which has more patient compliance.

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