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REVIEW OF FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT

The purpose of writing this review on floating drug delivery systems (FDDS) was to compile the recent literature with special focus on the principal mechanism of floatation to achieve gastric retention. The recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design ion exchange resin floating systems, and their classification also covered in detail. This project also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating systems, and natural and synthetic drug used in FDDS. In review also covered information about future Potential.

KEYWORDS: Floating Drug Delivery System, Ion Exchange Resin System.

INTRODUCTION

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. One difficulty is the inability to confine the dosage form in the desired area of the gastrointestinal tract. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Basic human physiology with the details of gastric emptying, motility patterns, and physiological and formulation variables affecting the cosmic emptying are summarized.[1] Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves

solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines.[2]

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of muco adhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying. Based on these approaches, classification of floating drug delivery systems (FDDS) has been described in the following sections.[3]

Effervescent floating drug delivery systems requires matrices prepared with swellable polymers such as methocel polysaccharides, e.g. Chitosan and effervescent components such as sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature.

Classification of Gastro Retentive Dosage Forms

The gastro retentive dosage forms can be classified as follows:

1 Expansive gastro retentive dosage form

The expanded structure is trapped in the stomach for prolong period leading to sustained drug release subsequent controlled absorption in stomach and intestine. When exposed to gastric environment capsule shell breaks and the dosage form attains its expanded structure, which is retained in stomach for longer time. Advantages of these systems include easy formulation, simple in operation and reproducible results however they suffer from serious drawback like clogging of pylorus end of stomach.[4]

2 Altered density dosage forms

Increasing the density from 1-1.6 prolongs the average time from 7-25 hrs. Gastric residence time can be improved by altering the density that is high density fast sedementating types and low density floating systems.[4]

3 High density or non floating drug delivery systems

This formulations are prepared by coating drug on a heavy core or mixed with heavy inert materials such as iron powder, zinc oxide, titanium dioxide or barium sulphate.

The following figure shows the multiunit high density dosage form sinking to the bottom in stomach.[4]

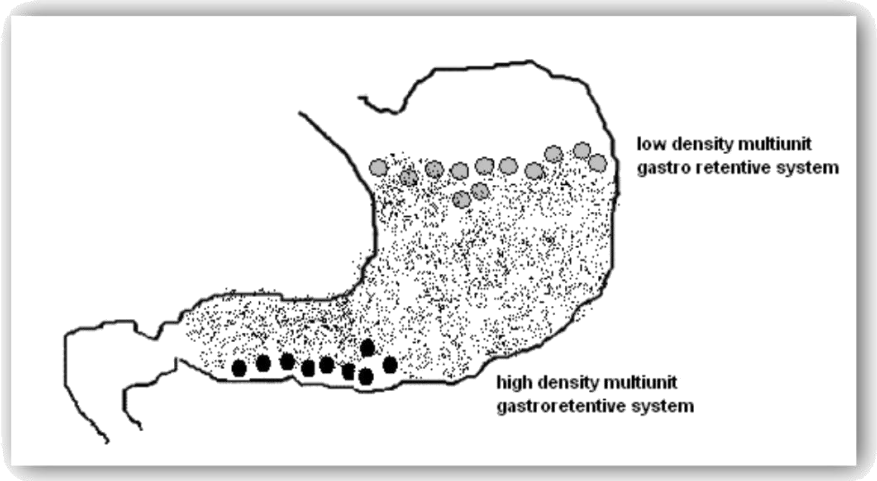

Figure 1: The Relative Positions of Floatable and Non-Floatable Multiunit Drug Delivery System in Stomach.

4 Low density or floating drug delivery system

FDDS either float due to their low density than stomach contents or due to the gaseous phase form inside the system after they come in contact with gastric environment.[4]

Depending Upon Working Principle of Fdds They Are Classified As

1. Non-Effervescent Floating Dosage Forms

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

1 Polycarbonate microspheres

Polycarbonate microspheres by solvent evaporation technique. Polycarbonate in dichloromethane was found to give hollow microspheres that floated on water and simulated bio-fluids as evidenced by scanning electron microscopy (SEM). High drug loading was achieved and drug-loaded microspheres were able to float on gastric and intestinal fluids. It was found that increasing the drug-to-polymer ratio increased both their mean particle size and release rate of drug.[5]

2 Floating alginate beads

Preparedfloating alginate beads incorporating amoxycillin. The beads were produced by dropwise addition of alginate into calcium chloride solution, followed by removal of gel beads and freeze-drying. The beads containing the dissolved drug remained buoyant for 20 hours and high drug-loading levels were achieved.[6]

3 Single-unit floating tablet

Single-unit floating tablets based on polypropylene foam powder and matrix-forming polymer. Incorporation of highly porous foam powder in matrix tablets provided density much lower than the density of the release medium. A 17% w/w foam powder (based on mass of tablet) was achieved in vitro for at least 8 hours. It was concluded that varying the ratios of matrix-forming polymers and the foam powder could alter the drug release patterns effectively.[7]

4 Floating micro particles

Floating micro particles of ketoprofen, by emulsion solvent diffusion technique. Four different ratios of Eudragit S 100 with Eudragit RL were used. The formulation containing 1:1 ratio of the 2 above-mentioned polymers exhibited high percentage of floating particles in all the examined media as evidenced by the percentage.[7]

5 HBS

HBS system containing a homogeneous mixture of drug and the hydrocolloid in a capsule, which upon contact with gastric fluid acquired and maintained a bulk density of less than1 thereby being buoyant on the gastric contents of stomach until all the drug was released (Figure 2).[8]

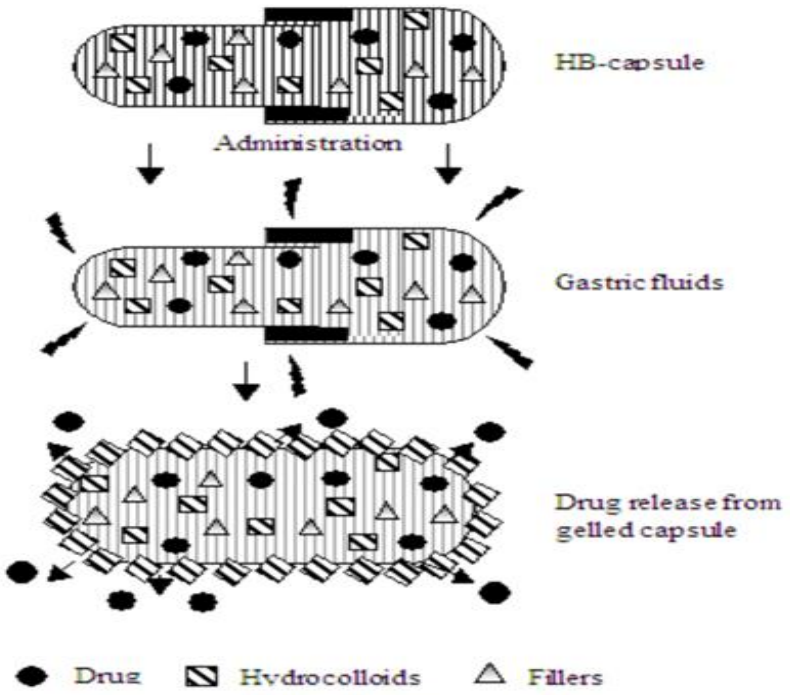

Figure 2: Working principle of hydro dynamically balanced system.

Hydro dynamically balanced sustained release tablets containing drug and hydrophilic hydrocolloids, which on contact with gastric fluids at body temperature formed a soft gelatinous mass on the surface of the tablet and provided a water-impermeable colloid gel barrier on the surface of the tablets. The drug slowely released from the surface of the gelatinous mass that remained buoyant on gastric fluids (Figure 3, A and B).[9]

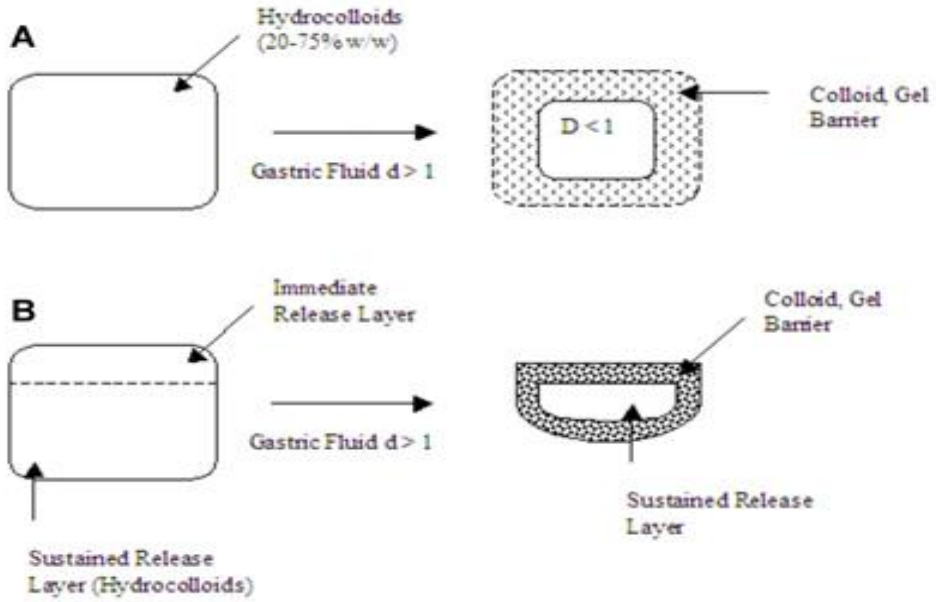

Figure 3: (A) United States patent 4 167 558, September 11, 1979.

(B) United States patent 4 140 755, February 20, 1979.

5. Controlled release tablets

Controlled release tablet of theophyllin have been developed using agar and light mineral oil. tablets were prepared by dispersing a drug and mineral oil mixture in a warm agar gel solution. This mixture was then poured into tablet moulds. On subsequent cooling and air drying floatable controlled release tablet wereformed.[9]

6. Controlled release powder

Controlled release powder formulations can either be compressed into tablet or filled into capsules. The formulations include a drug of basic nature, a water soluble salt of alginic acid and hydrocolloid gelling agent like HPMC, MC.

2 Effervescent Floating Dosage Forms

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, eg. sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms.

Floating System Using Ion Exchange Resine

A floatingsystem using ion exchange resin that was loaded with bicarbonate by mixing the beads with 1 M sodium bicarbonate solution. The loaded beads were then surrounded by a semipermeable membrane to avoid sudden loss of CO2. Upon coming in contact with gastric contents an exchange of chloride and bicarbonate ions took place that resulted in CO2 generation thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads (Figure 8). The in vivo behavior of the coated and uncoated beads was monitored using a single channel analyzing study in 12 healthy human volunteers by gamma radio scintigraphy. Studies showed that the gastric residence time was prolonged considerably (24 hours) compared with uncoated beads (1 to 3 hours).[10]

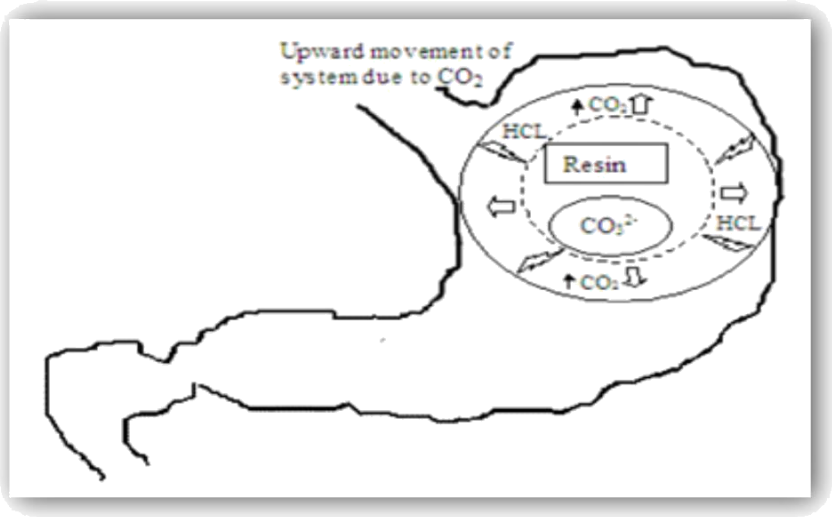

Figure 4: Pictorial presentations working of effervescent FDDS based on ion exchange resin.

Natural and Synthetic Drug Used In Floating Drug Delivery System

Floating of drug delivery system are also called as gastro-retentive drug delivery system that controlled the release of drug and prolong the retention time of drug in compression o the conventional drug by use various polymeric substance including natural polymer such as Guar gum, Xanthan gum, Gellan gum, or synthetic polymer such as HPMC (K4M, K15, K100M), Carbopol 934 polyvinyl alcohol, polyamides, polycarbonates, polymethylacrylic acid.[11]

Advantages of Floating Drug Delivery System

1. The gastroretensive system are advantageous for drug absorbed through the stomach. eg. Ferrous salts, Antacids.

2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirinand other similar drugs.

3. Administration of prolongs release floating dosage form, tablet or capsule will result of dissolution of the drugs in thegastric fluid. They dissolve in gastric fluid would available for absorption in small intestine after emptying of stomach content. it is therefore expected that drug fully absorbed fromfloating dosage form if it remains in the solution from even at the alkaline pH of the intestine.

4. The gastroretensive systems are advantageous for drugs meant for local action in the stomach. eg. Antacids.

5. When there is a vigorous intestinal movement and a short transit time as might occure in certain type of diarrhea. Poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.[12]

Disadvantages of Floating Drug Delivery System

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I tract.
2. These system requires a high level of fluid in the stomach for drug delivery to float and work efficiently-coat water.
3. The drugs that are significantly absorbed through out gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.[12]

Factors Affecting In Vitro and In Vivo Evaluation of Fdds

1 Physiological parameters

Age, sex, posture, food bio-adhesion, health of subject and g.i.t. condition.[13]

2 Galenic parameters

Diametrical size, flexibility, density of matrices.[13]

3 Control parameters

Floating type, Specific gravity, dissolution, hardness and friability (in case of tablets).[13]

Limitations

Apart from some attractive and inviting features of floating drug delivery system, they suffer from some disadvantages also. They require a sufficiently high level of fluid in stomach, for enabling system to float and to work efficiently. This limitation can be over by coating the dosage form with bio-adhesive polymers or alternatively by prescribing the dosage form. To be taken up with a glassful of water (200-250ml) FDDS are not suitable candidates for drug with stability or solubility problem in stomach. Some drugs like nifedipine, which is well absorbed along the entire G.I tract and undergoes extensive first pass metabolism may not be suitable for FDDS as the slow gastric emptying limits the systemic bioavailability. Drugs with irritant effect on gastric mucosa also limit the applicability of FDDS.[13]

Formulation development of (FDDS)

The major requirements for (FDDS) formulations are

1. It must form a cohesive gel barrier.
2. It must maintain specific gravity lower than gastric content (1.004-1.01 g/cc).
3. It should release content slowly to serve as a reservoir.

Evaluation of Floating Drug Delivery System

Various parameters that need to be evaluated in gastro-retentive formulations include floating duration, dissolution profiles, specific gravity, content uniformity, hardness, and friability in case of solid dosage forms. In the case of multiparticulate drug delivery systems, differential scanning calorimetry (DSC), particle size analysis, flow properties, surface morphology, and mechanical properties are also performed.

1. In Vitro Evaluation Parameters of Stomach Specific FDDS

Different studies can reported in the literature indicate that pharmaceutical dosage forms exhibiting gastric residence in vitro floating behavior shows prolonged gastric residence in vivo. Although in vitro floating behavior alone is not sufficient proof for efficient gastric retention so in vivo studies can provide definite proof that prolonged gastric residence is obtained.

1. Floating Lag Time and Total Floating Time Determination

The time between the introduction of tablet into the medium and its rise to upper one third of the dissolution vessel is termed as floating lag time and the time for which dosage form floats is termed as the floating and floatation time. These tests are usually performed in stimulated gastric fluid or 0.1 mole lit^{-1} HCL is maintained at 37^0C, by using USP dissolution apparatus containing 900 ml of 0.1 molar HCL as the dissolution medium.

2. Drug Release

The test for in vitro drug release studies are generally carried out in stimulated gastric and intestinal fluid maintained at 37^0C. Dissolution tests are performed using he USP dissolution apparatus, samples are withdraw periodically from dissolution medium, replaced with same volume of fresh medium each time, and then analysed for their drug content after an appropriate dilution.

3. Resultant Weight Determination

Bulk density and floating duration have been main parameters to describe the adequacy of dosage form's buoyancy although single density determination dose not predict force evaluation of the dosage form because the dye material of it is made progressively reacts or interacts with in the gastric fluid to release its contents.

4. X-Ray/ Gamma Scientigraphy

For in vivo studies, X-Ray gamma scientigraphy is the main evaluation parameter for floating dosage form. In each experiment the animals are allowed to fast overnight with free access to water, and radiograph is made just before the administration of the floating tablet to ensure the absence of radio opaque material, Visualization of dosage form X-Ray is due to the inclusion of a swallowing followed by 50 ml of water. The radiographic imaging is taken from each animal in standing position and the distance between source of X-Ray and the animal should kept constant for all imaging, so that the tablet movement could be easily noticed. Gastric radiography was done at 30-min time intervals for a period of 5 hr using an X-Ray machine.

5. Pharmacokinetic Studies

Pharmacokinetic studies include (AUC) Area Under Curve, Cmax and time to each maximum plasma concentration (Tmax) were estimated using a student t test with p, 0.05 as the minimal level of significance.

6 Specific Gravity

Displacement method is used to determine the specific gravity of floating system using benzene as a displacing medium.

7 Drug Loading, DEE, Particle Size Analysis, Surface Characterisation, Micrometric Studies, Percentage Yield, (For Floating Microspheres and Beads)

Drug loading assessed by crushing accurately weighed samples of beads or microspheres in a mortar and added to the appropriate dissolution medium which is then centrifuged, filtered and analysed by various analytical method like spectrophotometry. The percentage loading is calculated by dividing the amount of drug in the sample by the weight of total beads or microspheres. The particle size and size distribution of beads or microspheres are determined in the dry state using the optical microscopy method. The external and cross-sectional morphology (Surface characterization) is done by SEM.[14]

Applications of Floating Drug Delivery System

Floating drug delivery offers several advantages for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.[1]

1. Sustained Drug Delivery

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibit. Recently sustained release floating capsule of nicardipine hydrochloride was developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsule using rabbits.

2. 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, eg. riboflavin and furosemide.

Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets.

A bi-layer-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. By targeting slow delivery of misoprostol to the stomach, desired therapeutic levels could be achieved and drug waste could be reduced.[15]

Future Potential

Floating dosage forms offer various potential advantages for drug with poor bioavailability because their absorption is restricted to the upper G.I. tract and they can be delivered efficiently thereby maximizing their absorption and enhancing their absolute bioavailability it has been reported that para-amino-benzoic acid, a drug with limited absorption site in the G.I.

showed 1.61times greater AUC in case of floating pills compared with conventional pills for some drugs like iso-sorbide 5-nitrate, which is well absorbed from both the stomach and intestine. The floating system didn't show significant difference in bioavailability as compared to control pills.

Thus in terms of bioavailability, prolonging the GRT of a dosage form containing drugs having multiple absorption sites in the G.I. tract offers no advantages. Oral insulin and other oral dosage forms can be improved by FDDS.

CONCLUSION

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach for gastric retention. Although there are number of difficulties to be worked out to achieve prolonged gastric retention, a large number of companies are focusing toward commercializing this technique. But these dosage forms can serve as a potential option to formulate a drug so that they can retain themselves in the G.I.T beside this these dosage forms can be of wide application in the case of obligatory oral dosage forms and when the patient is suffering from rapid gastric emptying. Thus this dosage forms promises us reliable answers to the questions that will be encountered while developing the dosage forms with stringent limitations.

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