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REVIEW ARTICLE

Floating Drug Delivery System: A New Approach

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ABSTRACT

Floating drug delivery system (FDDS) helps to improve the buoyancy property of the drug over the gastric fluids and hence maintain the longer duration of action. The aim of the present study is on floating drug delivery systems (FDDS) was to compile the recent literature with particular focus on the main floating mechanism to achieve gastric retention. Floating multi-particulate are gastro-retentive drug delivery systems which are based on non-effervescent and effervescent approach. This type of drug delivery method would have comparatively less side effect and would eliminate the need for repeated dosages.

Keywords: Floating drug delivery System(FDDS), Drug Delivery, Sustain release, Methods.

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INTRODUCTION

Floating drug delivery system is the main approaches to prolonging the gastric residence time in the stomach. he basis behind FDDS is making the dosage form less dense than the gastric fluids to make it float on them. Prolonging the gastric retention of a delivery system is desirable for achieving the greater therapeutic efficacy of the drug substance under certain circumstances. Floating Oral Drug Delivery System (FDDS) are retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids.[1,2] In pharmaceutical dosage, the formulation of drugs in multilayered / bi-layered tablets is a innovative approach for providing the loading dose and maintenance dose in a tablet. Polymers have the main role in the development of FDDS, which serve as carriers for the drug and determine the gastric retention time and drug protection. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.[3,4]

Advantages

1. FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhoea to keep the drug in floating condition in stomach to get a relatively better response.
2. The drugs which are absorbed through the stomach, for them the gastro- retentive system is advantageous. E.g., Ferrous salts, and antacids.[5]

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3. It is useful in treating gastroesophageal reflux disorder (GERD).[6].
4. Improved drug absorption with increased GRT and excess duration of contact of dosage regimen at its target site.
5. FDDS are advantageous for those drugs which provide local irritation to the stomach. eg: Antacids.
6. FDDS improves patient compliance by decreasing dosing frequency.
7. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration are avoided; a desirable plasma drug concentration is maintained by continuous drug release.
8. Better therapeutic effect of short half-life drugs can be achieved.
9. Gastric retention time is increased because of buoyancy.
10. Enhanced absorption of drugs which solubilize only in stomach.

11. Superior to single unit floating dosage forms as Such microsphere's releases drug uniformly and there is no risk of dose dumping.

Classification of floating drug delivery system[7-11]

Single Unit Floating Dosage Systems (Figure 1)
a) Effervescent Systems (Gas-generating Systems)
b) Non-effervescent Systems

Multiple Unit Floating Dosage System
a) Effervescent Systems (Gas-generating Systems)
b) Non-effervescent Systems
c) Hollow Microspheres

a) Effervescent Systems (Gas-generating Systems)

Effervescent These buoyant systems utilized matrices prepared with swellable polymers like HPMC, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifiers at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating, which is insoluble but permeable, allows permeation of water (Figure 2a). Thus, carbon dioxide is released, causing the beads to float in the stomach. Excipients used most commonly in these systems include HPMC, poly acrylate polymers, polyvinyl acetate, Carbopol®, agar, sodium alginate, calcium chloride, poly ethylene oxide and polycarbonates[12] system floating drug delivery system These are complex drug delivery systems consisting of a type of matrix and an inflatable polymer such as methylcellulose and chitosan, along with effervescent compounds. Bicarbonate of sodium, tartaric acid, citric acid. When CO_2 comes into contact with acidic gastric contents, it is generated and stuck in swollen hydrocolloids, giving dosage types buoyancy (Figure 2b).

b) Non-effervescent Systems

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the 'plug type systems' since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one with in the outer gelatinous barrier. The air trapped by the

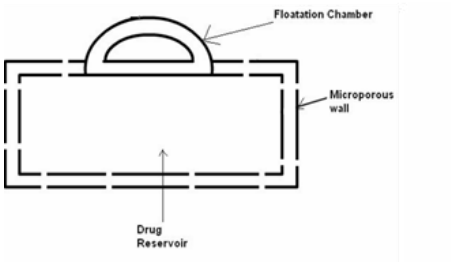

Figure 1: Single Unit Floating Dosage Systems

swollen polymer confers buoyancy to these dosage forms. Examples of this type of FDDS include colloidal gel barrier, microporous compartment system, alginate beads, and hollow microspheres. Another type is a Fluid-filled floating chamber which includes incorporation of a gas-filled floatation chamber into a micro porous component that houses a drug reservoir. Polysaccharides, hydrocolloids, and matrix-forming polymers such as polyacrylate, polycarbonate, polystyrene, and polymethacrylate are used to generate a gel-forming or swelling cellulose type in non-effervescent floating dosage forms.

Multiple Unit Floating Systems

Inspite of extensive research and development in the area of HBS and other floating tablets, these systems suffer from an important drawback of high variability of gastrointestinal transit time, when orally administered, because of their all or nothing gastric emptying nature. In order to overcome the above problem, multiple unit floating systems were developed, which reduce the inter-subject variability in absorption and lower the probability of dose dumping. Reports have been found on the development of both non-effervescent and effervescent multiple unit systems. Much research has been focused and the scientists are still exploring the field of hollow microspheres, capable of floating on the gastric fluid and having improved gastric retention properties.[13]

Non-effervescent Systems

No much report was found in the literature on non-effervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported. A mixture of drug, chitosan and acetic acidic extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates and floats in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio.[14,15]

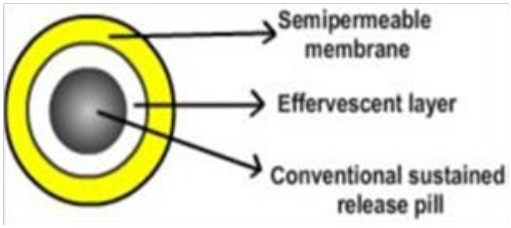

Figure 2(a): Different layers-Semi permeable membrane, Effervescent Layer

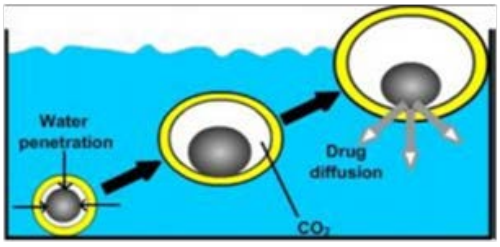

Figure 2(b): Mechanism of floatation via CO_2 generation

B) Effervescent Systems (Gas-generating Systems)

There are reports of sustained release floating granules containing tetracycline hydrochloride. The granules are a mixture of drug granulates of two stages A and B, of which A contains 60 parts of HPMC,40parts of poly acrylic acid and 20parts of drug and B contains 70 parts of sodium bicarbonate and 30 parts of tartaric acid.60 parts by weight of granules of stage A and 30 parts by weight of granules of stage B are mixed along with a lubricant and filled in to capsule. In dissolution media, the capsule shell dissolves and liberates the granules, which showed a floating time of more than8handsustained drug release of 80% in about 6.5 h. Floating mini capsules of pepstatin having a diameter of 0.1-0.2 mm has been reported by Umezawa[16].These mini capsules contain a central core and a coating. The central core consists of a granule composed of sodium bicarbonate, lactose and a binder, which is coated with HPMC. Pepstatin is coated on the top of the HPMC layer. The system floats because of the CO_2 release in gastric fluid and the pepstatin resides in the stomach for prolonged period. Alginates have received much attention in the development of multiple unit systems. Alginates are non-toxic, biodegradable linear copolymers composed of L-glucuronic and L-mannuronic acid residues.

A multiple unit system was prepared comprises of calcium alginate core and Calcium alginate / PVA membrane, both separated by an air compartment. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and concentration of PVA, resulted in enhancement of the floating properties of the system.[17,18]

Freeze-drying technique is also reported for the preparation of floating calcium alginate beads. Sodium alginate solution is added drop wise into the aqueous solution of calcium chloride, causing the instant gelatin of the droplet surface, due to the formation of calcium alginate. The obtained beads are freeze-dried resulting in a porous structure, which aid in floating. The authors studied the behaviour of radio labelled floating beads and compared with non-floating beads in human volunteers using gamma scintigraphy. Prolonged gastric residence time of more than 5.5 h was observed for floating beads. The non-floating beads had a shorter residence time with a mean on set emptying time of 1-hour.

A new multiple type of floating dosage system had developed having a pill in the core, composed of effervescent layers and swellable membrane layers coated on sustained release pills (shown in figure). 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. These sub layers were surrounded by a swellable polymer membrane containing polyvinyl acetate an purified shellac. When this system was immersed in the buffer at 37°C, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO_2 was generated by the neutralization reaction between the 2 effervescent agents, producing swollen pills (like balloons) with a density less than1.0g/ml.[19]

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. The general techniques involved in their preparation include simple solvent evaporation and solvent diffusion and evaporation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers such as polycarbonate, Eudragit® Sand cellulose acetate were used in the preparation of hollow microspheres, and the drug release can be modulated by optimizing the polymer quantity and the polymer-plasticizer ratio. Sustained release floating microspheres using polycarbonate were developed, employing solvent evaporation technique. Aspirin, griseofulvin and p-nitroaniline were used as model drugs. Dispersed phase containing polycarbonate solution in dichloromethane, and micronized drug, was added to the dispersion medium containing sodium chloride, polyvinyl

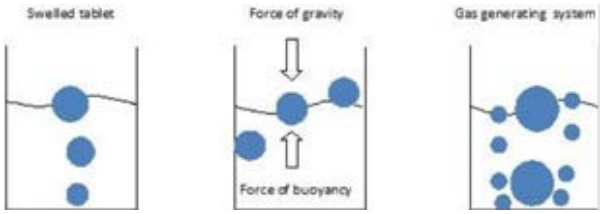

Figure 3: Different mechanisms of floating systems.

alcohol and methanol. The dispersion was stirred for 3-4 hours to assure the complete solvent evaporation, and the microspheres obtained were filtered, washed with cold water and dried. The spherical and hollow nature of the microspheres was confirmed by Scanning electron microscopic studies.[20,21]

Drug incorporated is found to influence the particle size distribution and drug release. The larger proportion of bigger particles was seen a thigh drug loading which can be attributed to the increased viscosity of the dispersed phase.

C. Raft Forming Systems

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The basic mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, where in each portion of the liquid swells forming a continuous layer called a raft (Figure 3). The raft floats because of the buoyancy created by the formation of CO2 and act as a barrier to prevent the reflux of gastric Contents like HCl and enzymes into the oesophagus. Usually, the system contains age l forming agent and alkaline bicarbonates or carbonates responsible for the formation of to make the system less dense and float on the gastric fluids.[22]

Factors influencing the delivery mechanism for floating drugs

1. Density of the dosage form

Floating dosage form density is a buoyancy property of the dosage form that depends on the density. The density of the dosage type (1.004gm/ml) should be less than the gastric content. To exhibit floating property, a density of less than 1.0 gm/cm3 is required. Therefore, dosage types will float to the surface with a density lower than the gastric content, whereas systems of high density sink to the bottom of the stomach.[23]

2. Dosage form shape and size

Other factors that affect gastric retention are the shape and size of the dosage form. Increases in GRT relative to those with a diameter of 9.9 mm are recorded in dosage type units with a diameter greater than 7.5 mm. With a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI), the dosage form with tetrahedron and ring shape designs was stated to exhibit better GIT for 90 to 100% 24 hours retention compared to other shapes.[24]

3. Ingestion of food and its composition

Feed intake, food viscosity and volume, caloric content and feeding frequency have a significant effect on the stomach retention of dosage types. The gastric retention time (GRT) of the dosage type is affected by the presence or lack of food in the gastrointestinal tract (GIT). Feeding indigestible polymers or fatty acid salts may alter the stomach motility pattern to a fed state, resulting in a decreased rate of gastric emptying and prolonged release of drugs.[25]

4. Caloric material with a meal rich in protein and fat, gastric retention time (GRT) can be increased by 4 to 10 hours. Due to the low frequency of migrating myoelectric complexes, floating will increase by over 400 minutes when successive meals are given compared to a single meal (MMC).[26]

5. Gender, posture and age effects Females experience slower rates of gastric emptying than males. The influence of posture does not vary much more in the mean time of gastric retention (GRT). Gastric emptying is slowed down in the case of elderly individuals, especially those over 70, who have a significantly longer GRT. Medication distribution is often impaired by disease conditions such as diabetes and Crohn's disease etc.[27]

6. Single or multiple formulation for units leading to the failure of the units, multiple unit formulations are more predictable, allow coadministration of units with different release profiles or containing incompatible substances and allow a greater safety margin against failure of the dosage form compared to single unit dosage forms.

7.Particle size: To pass through the pyloric valve into the small intestine, the particle size should be 1 to 2 mm

8. Emotional state of subject: The influence of emotional factors on gastric motility and secretion may be either Augmentative or inhibitory depending upon whether the emotional experience is of an aggressive or a depressive.[28]

9. Exercise: physical activity retards gastric emptying.

10. Disease states: Diseases like gastroenteritis, gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastric emptying. Partial or total gastrectomy, duodenal ulcer and hyperthyroidism promote gastric emptying rate.[29]

11.Frequency of Feed: The GRT can increase over by 400 times when successive meals are given compared with a single meal due to the low frequency of MMC.

Future Potential

FDDS approach may be used for various potential active agents with narrow absorption window, e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines) which are absorbed from very specific regions of GI tract and whose development has been halted due to the lack of appropriate pharmaceutical technologies. In addition, by continual supplying the drug to its most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropoietin, vasopressin, insulin, low molecular weight heparin, and LHRH. Some of the unresolved critical issues related to the rational development of FDDS include, the quantitative efficiency of floating delivery systems in the fasted and fed states and the correlation between prolonged GRT and SR/ PK characteristics. However, we are as close as we have ever been to see a greater transition of gastric retention devices from developmental level to the manufacturing and commercial level.

Diabetes mellitus is one of the most common endocrine diseases in all populations and all age groups. It is a syndrome of disturbed intermediary metabolism caused by inadequate insulin secretion or impaired insulin action, or both. Diabetes mellitus comprises of heterogeneous group of disorders characterized by hyperglycaemia, altered metabolism of carbohydrates, lipids and proteins. Diabetes mellitus is associated with complications such as nephropathy, retinopathy, neuropathy and cardiovascular disease.

CONCLUSION

A current endeavor is the development of an effective gastro-retentive dosage form for stomach-specific medication delivery. As a result, numerous ways were attempted to achieve the desired gastro retention, with the floating medication delivery system emerging as the most promising. 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.

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