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Review Article

A Review on Emerging Floating Drug Delivery System

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ABSTRACT

Presently, various approaches have been exploited in the prolongation of gastric residence time which includes floating drug delivery system (FDDS), swelling and expanding systems, bio-adhesive systems, modified shape systems and high density systems. Among various methods, floating drug delivery system is considered to be a predominant method. Gastric emptying of dosage forms is an extremely varying process and ability to extend and control the emptying time is a valuable resource for the dosage forms. This FDDS is having the ability to provides a solution for this purpose. The FDDS is a bulk density system lower than the gastric fluid, so that the rest will float on the stomach contents for a prolonged period of time and allowing the drug to release slowly at a desired rate from the system and intensifies the bio-availability of the drug having narrow absorption window. The main intension of writing this review on floating drug delivery system is to study the mechanism of flotation to acheive the gastric retention and to discuss briefly about the background of FDDS, advantages and disadvantages, application of FDDS and factors affecting the gastric retension time.

Keywords: Floating drug delivery system (FDDS), Oral route of drug delivery, Classification of FDDS, Mechanism of FDDS, Factors affecting FDDS, Sustained release.

INTRODUCTION

A drug delivery system (DDS) is characterized as a formulation or a device that allows the initiation of a therapeutic substance in the body and raising its ability to produce a desired effect and protecting it by controlling the rate, time and place of release of drugs in the body. This mechanism composed of the introduction of the therapeutic product, the release of the active contents by the product, and the successive moving of the active ingredients across the biological membranes to the site of action[1]. In the current years, due to the necessities of clinical therapy, the development of relevant carriers for controlled drug delivery is a difficult task for the researchers. Some of the antibiotics, proteins, peptides, drugs are unstable compounds and need to be secured from the degradation in biological environment[2]. The future of these molecules as a therapeutic agent clearly relies on the design of a suitable carrier for its delivery into the body. Several studies have been reported so far in the improvement of these carriers, among which the design of biodegradable micro particles has drawn extensive considerations[3]. A microencapsulated drug is a promising drug delivery system having distinct advantages, such as increasing therapeutic efficiency and efficacy, prolonging the biological activity, controlling the drug release rate and decreasing the administration frequency[4]. The most vital criteria of the lattice material ought to be biodegradable inside a specific timeframe which ought to be versatile with the medication discharge rate. Henceforth, the biodegradable polymers have been the significant centre of push to accomplish enhanced conveyance frameworks in pharmaceutical examination[5]. Among the distinctive classes of biodegradable polymers, for example, Polylactic corrosives, Polyethylene glycol, Polylactic glycolic acid, Chitin, Chitosan, Starch and Polyethylene oxide have produced enormous interest in view of their magnificent biocompatibility, biodegradability and mechanical quality[6]. They are anything but difficult to plan into different gadgets for conveying an assortment of medication classes, for example, anti-microbials, proteins, immunizations, peptides and miniaturized scale particles[7].

Route of administration

Drug might be brought into the human body by various anatomical courses. They might be foreordained for systemic impacts or focused to different organs and diseases. The favoured route of administration relies ~~on~~ upon the malady, the impact desired and the product accessible. Drugs might be managed specifically to the organ influenced by malady or given systemically and focused to the ailing organ[8]. Besides there are physiological contemplations that regularly block the utilization of certain route of administration which are unsteady in the gastrointestinal tract or medications which experience broad first pass impact and not appropriate for oral administration. For instance, insulin is obliterated in the stomach and medications like Xylocaine and Nitroglycerine are not reasonable for oral organization because of the quick evacuation of the medication by first-pass impact[9]. Besides, certain medications are not pertinent for organization intramuscularly because of whimsical medication discharge, torment or nearby disturbance. Despite the fact that the medication is infused into the bulk, the medication must achieve the circulatory system or other body liquid to end up bioavailable. The

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anatomic site of the intramuscular infusion will influence the rate of medication ingestion[10]. All in all, the strategy for medication administration which is more trustworthy and which contribute a biggest bioavailability ought to be given to guarantee most extreme restorative impact[11]. Intravenous organization is the brisk and more unsurprising method for conveying the medication into the circulatory system. Drug controlled extravascularly is caught up in the circulatory system and the aggregate retained measurement is dispensed with gradually. Intramuscular infusions by and large bear the cost of more fast retention than the oral organization of arrangements which are inadequately dissolvable. Be that as it may, precipitation of the medication at the infusion site may bring about slower assimilation and a deferred reaction[12].

Oral route of administration

An oral drug delivery system is the most alluring course of organization of the medication[13,14]. Oral drug delivery stays well in front of the pack as the favoured conveyance route because of its flexibility, simplicity of organization and above all patient consistence[15,16]. Oral drug delivery system requires advancement in materials science:

- To give materials biocompatibility amid delayed contact with body tissues,
- Bioengineering to create drug conveyance modules,
- Clinical pharmacology for clarification of medication activity under states of constant

For expense and patient accommodation, oral conveyance is totally an appealing technique[17-19]. Drug that are effectively retained from the gastro intestinal tract have a short organic half-life and wiped out rapidly from the blood dissemination consequently requires incessant dosing[20]. To keep away from this issue, the oral controlled discharge plans have been created trying to discharge the medication gradually into the gastro intestinal tract (GIT) and keep up a consistent medication focus in the serum for more timeframe[21]. For the controlled release systems, the oral route of administration is exceptionally favoured. Persistent acknowledgment of the oral route is quiet high[22]. It is a safest route of administration contrasted with the parenteral route and the imperatives of sterility and potential harm at the site of organization are insignificant[23]. The larger part of oral controlled release, drug delivery systems relies on upon disintegration, dissemination or a mix of both instruments for moderate arrival of medication[24]. To expand the gastric emptying time and control over the arrival of the medication from the devices, the expanding self-control of conveyance innovation will guarantee the advancement of expanding number of gastro retentive drug delivery systems to streamline the conveyance of particles that display low bioavailability and broad first pass metabolism[25].

Mechanism of Floating Durg Delivery System

Floating drug delivery system is additionally called as the hydro dynamically balanced system (HBS). FDDS have a mass density which is not exactly the gastric liquid substance and subsequently stay buoyant in the stomach for a delayed timeframe without influencing the gastric exhausting rate. This outcome in the expansion of gastric residence time (GRT) and a superior control of the vacillations in plasma drug focus[14,26-29]. FDDS served as a brilliant medication conveyance system for the annihilation of Helicobacter pylori, which is currently accepted to be causative bacterium for constant gastritis and peptic ulcers. The patients require high convergence of the medication to be kept up at the site of contamination that is inside the gastric mucosa. The floating measurements structure by uprightness of its floating capacity is held in stomach and keeps up the high grouping of the medication at stomach[30]. A sustained liquid arrangement of ampicillin was created utilizing sodium alginate that spreads out and sticks to gastric mucosal surfaces whereby discharging the medication ceaselessly over a timeframe[31]. The mechanism of the floating drug delivery system is represented in the Figure 1. Floating drug delivery systems are especially helpful for corrosive stable medications, drugs which are ineffectively solvent or unstable in intestinal liquids and for the medications which experience unexpected changes in their pH-subordinate dissolvability because of nourishments, age and way physiological states of GIT[32]. Parkinson's ailment can be treated with the floating system by utilizing furosemide by which roughly 30% of the medication is consumed by oral organization[33]. The majority of the medications when regulated orally have a high disintegration rate in the stomach which results in the poor bioavailability of the medication, while the remaining measure of the medication is discharged out[34]. As a consequence of the directed measurement's fast GI travel, complete medication retention is averted in the ingestion zone and decreases adequacy of the controlled dosage, since most of the medications are caught up in the stomach or in the upper part of the small digestive tract[35]. The controlled gastric maintenance of strong dose structures might be accomplished by the components of mucoadhesion, buoyancy, sedimentation, development, altered shape frameworks, or by the synchronous organization of pharmacological specialists that defer the gastric exhausting[36]. In light of these methodologies, grouping of floating drug delivery systems (FDDS) has been portrayed in subtle element. Invivo/invitro assessment of FDDS has been talked about by different analysts to evaluate the productivity and utilization of such systems. A few delayed cases have been accounted for demonstrating the effectiveness of such frameworks for medications with bioavailability issues[37-39]. The swelling mechanism is described in the Figure 2.

Advantages of FDDS

- Gastro retentive medication conveyance can minimize the counter movement of the body driving to higher medication proficiency.
- They likewise have preference over their conventional system as it can be utilized to beat the difficulties of the gastric maintenance time (GRT) and additionally the gastric emptying time (GET).
- When there is a basic intestinal development and a short travel time as happen in certain kind of looseness of the
- bowels, poor ingestion will be anticipated. Under such circumstances, this system might be useful to keep the

medication in floating condition in stomach to get a moderately better reaction.

- Acidic substances like aspirin cause aggravation on the stomach wall when it comes in contact with stomach wall. Thus floating drug conveyance definition might be helpful for the organization of ibuprofen and comparative different medications.

Disadvantages of FDDS

- The floating require an adequate abnormal state of liquids in the stomach for the system to float and to discharge sedate locally in the stomach.
- Floating systems is not relevant for those medications that have dissolvability or dependability issue in gastro intestinal tract.
- Some medications of floating system will make irritation to gastric mucosa.
- The medication that are fundamentally assimilated all through gastrointestinal tract, which experience huge first-pass metabolism[40].

Classification of Floating Drug Delivery System

Based on the mechanism of buoyancy, two distinctly different technologies, i.e. non-effervescent and effervescent systems, have been utilized in the development of floating drug delivery systems.

Non-Effervescent Floating Drug Delivery Systems

The most normally utilized non-effervescent floating drug delivery systems are gel shaping or profoundly swellable cellulose sort hydrocolloids, polysaccharides, and lattice framing polymers, for example, polycarbonate, polyacrylate, polymethacrylate, polystyrene and so on. One of the methodologies for its definition of such floating dose frames includes private blending of medication with a gel shaping hydrocolloid, which swells in contact with gastric fluid after oral organization and keeps up a relative uprightness of shape and a mass thickness of not as much as solidarity inside the external coagulated obstruction. The air caught by the swollen polymer gives lightness to these measurement frames. Moreover, the gel structure goes about as a store for supported medication discharge following the medication is gradually discharged by a controlled dissemination through the coagulated obstruction[36,41,42]. In 1978, Sheth and Tossounian proposed that when such dose shapes interact with a watery medium, the hydrocolloid begins to hydrate by framing a gel at the surface of the dose structure. The resultant gel structure then controls the rate of dispersion of dissolvable in and drug-out of the measurements structure. As the outside surface of the dose structure goes into arrangement, the gel layer is kept up by the prompt nearby hydrocolloid layer getting to be hydrated[43]. Accordingly, the medication breaks up in and diffuses out with the diffusing dissolvable, making a 'subsiding limit' inside the gel structure. The different sorts of this system are as per the following:

Single Layer Floating Tablets

They are figured by personal blending of medication with gel-shaping hydrocolloid, which swells when goes ahead contact with the gastric liquid and keeps up a mass thickness of not as much as solidarity. The air caught by the swollen polymer presents buoyancy to this dose shapes[44].

Bilayer Floating Tablets

A bilayer tablet contains two layers with a quick discharge layer which discharges starting dosage from framework by disintegration works the another managed discharge layer assimilates gastric liquid, shaping an impermeable colloidal gel hindrance on its surface, and keeps up a mass thickness of not as much as solidarity and along these lines it stays buoyant in the stomach and discharge the medication by dispersion[44,45].

Alginate Beads

Multi unit floating measurements structures are created from freeze-dried calcium alginate. Spherical beads of roughly 2.5 mm breadth can be set up by dropping a sodium alginate arrangement into watery arrangement of calcium chloride, bringing about precipitation of calcium alginate prompting development of permeable framework, which can keep up a floating power for more than 12 hours. At the point when contrasted and strong beads, which gave a short residence, time of 1hour, and these floating beads gave a delayed residence time of over 5.5 hours[46,47].

Hollow Microspheres

Hollow microspheres (microballons), stacked with medication in their external polymer shells were set up by an emulsion dissolvable dissemination technique (emulsion solvent diffusion method. The ethanol: dichloromethane arrangement of medication and enteric acrylic polymer were filled a disturbed watery arrangement containing PVA and the resultant blend is thermally controlled at 40^{o} C. The gas stage is created in the scattered polymer by the dissipation of dichloromethane structures an inward hole in microsphere stacked with medication. The smaller scale inflatables shaped can drift persistently over the surface of acidic disintegration media containing surfactant for over 12 hours by invitro[48-50].

Effervecent Floating Drug Delivery Systems

These buoyant conveyance systems use lattices arranged with

- Swellable polymers, for example, methocel or polysaccharides, e.g., Chitosan,
- Other foaming parts, e.g., sodium bicarbonate and potassium bicarbonate
- Lattices containing assemblies of fluid that gasifies at body temperature.

The lattices are created so that upon entry in the stomach, carbon dioxide is freed by the sharpness of the gastric substance and is ensnared in the gellified hydrocolloid. This creates an upward movement of the measurement structure to float on the chime[51-54]. In 2002 Choi et al prepared the floating alginate beads using gas-forming agents (calcium carbonate and sodium bicarbonate) and studied the effect of CO_2 generation on the physical properties, morphology and release rates. The study shows that the kind and amount of gas-forming agent had a profound effect on the size, floating ability, pore structure, morphology, release rate and mechanical strength of the floating beads. It was concluded that calcium carbonate forms a smaller but stronger beads than sodium

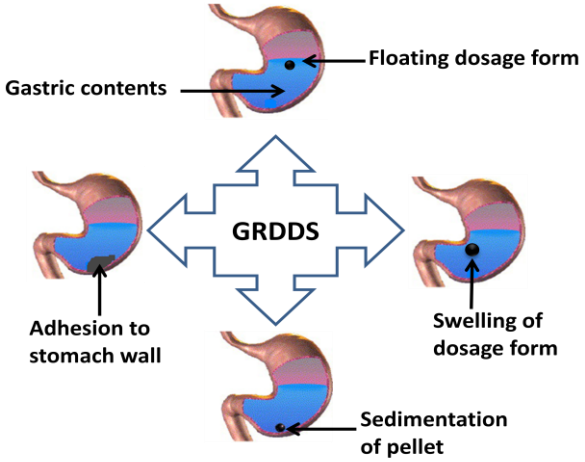

Figure 1: Mechanism of floating drug delivery system (Deepak.A et al, 2012).

bicarbonate. Calcium carbonate is found to be a less-effective gas-forming agent than sodium bicarbonate but it can produce superior floating beads with enhanced control of drug release rates[55].

The effervescent systems are further divided into:

- Gas generating systems
- Volatile liquid/vacuum systems

Gas Generating Systems

Intra Gastric Single Layer Floating Tablets or Hydro dynamically Balanced System (HBS)

The HBS have a mass thickness lower than the gastric liquid so it stays in the stomach for a drawn out timeframe without influencing the gastric liquid (Figure.3). The medication is gradually discharged at a craved rate from the drifting system and after the complete discharge the leftover system is expelled from the stomach. This prompts an expansion in the gut and a superior control over variance in plasma drug fixation[56,57].

Intra Gastric Bilayer Floating Tablets

These are also compressed as a tablet as shown in the figure and it contains two layers (Figure.4)[58] i.e.,

- Immediate release layer and
- Sustained release layer.

Multiple Unit type floating system

This system comprise of supported discharge pills as "seeds" encompassed by twofold layers and is described in Figure 5 and Figure 6. The inward layer comprises of foaming specialists while the external layer is of swellable film layer. At the point when the framework is inundated in disintegration medium at body temperature, it sinks on the double and after that structure swollen pills like inflatables, which floats since they have lower thickness. This lower thickness is because of the era and ensnarement of CO_2 inside the system[42].

Volatile Liqiud / Vaccum Containing System

Intragastric Floating Gastrointestinal Drug Delivery System

This system can be made to float in the stomach because of floatation chamber, which might be a vacuum or loaded with air or a safe gas, while drug store is typified inside a miniaturized scale permeable compartment[32]. The working principle of this system is clearly illustrated in the Figure 7.

Inflatable Gastrointestinal Delivery Systems

This framework contains inflatable chamber, which contains liquid ether that gasifies at body temperature to bring about the chamber to blow up in the stomach (Figure 8). These frameworks are manufactured by stacking the inflatable chamber with a medication store, which can be a medication impregnated polymeric network, which is typified in a gelatin case. After oral organization, the gelatin container breaks down to discharge the medication repository together with the inflatable chamber. The inflatable chamber consequently swells and holds the medication supply into the gastric liquid[59].

Intragastric osmotically Controlled Drug Delivery System

It is involved an osmotic weight controlled medication conveyance gadget with an inflatable gliding support in a biodegradable case (Figure 9). In the stomach, the case rapidly breaks down to discharge the intragastric osmotically controlled medication conveyance gadget. The inflatable backing present inside forms a deformable empty polymeric sack that contains a fluid which gasifies at body temperature to blow up the pack. The osmotic weight controlled medication conveyance gadget comprises of two segments: drug store compartment and an osmotically dynamic compartment[60]. The medication store compartment is encased by a weight responsive collapsible sack, which is impermeable to vapour and fluid and has a medication conveyance opening. The osmotically dynamic compartment contains an osmotically dynamic salt and is encased inside a semipermeable lodging. In the stomach, the water in the GI liquid is persistently consumed through the semipermeable film into osmotically dynamic compartment to break down the osmotically dynamic salt. An osmotic weight is then made which follows up on the collapsible pack and thusly compels the sack supply compartment to lessen its volume and enacted the medication discharge through the conveyance hole[61]. The floating support is also made to contain a bioerodible plug that erodes after a predetermined time to deflat the support. The deflated drug delivery system is then emptied from the stomach[62,63].

Factors Affecting Gastric Retention

Different endeavours have been made to hold the measurement structure in the stomach as a method for expanding the maintenance time. These endeavours incorporate utilization of floating drug delivery systems, mucoadhesive systems, high-density systems, adjusted shape frameworks, gastric-emptying delaying devices and co-organization of gastric-emptying delaying drugs. The majority of these methodologies are impacted by various variables that influence their bioavailability and viability of the gastro retentive system[64]. Some of the factors are listed below:

Density

Gastric residence time (GRT) is a component of measurement structure lightness which wards on its thickness. A buoyant dose structure is having a density of not as much as that of the gastric fluids floats. Since it is far from the pyloric sphincter, the dose unit is held in the

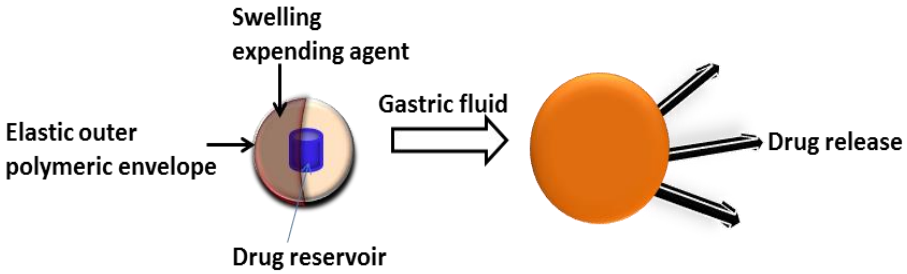

Figure 2: Mechanism of swelling (K Kavitha et al 2011).

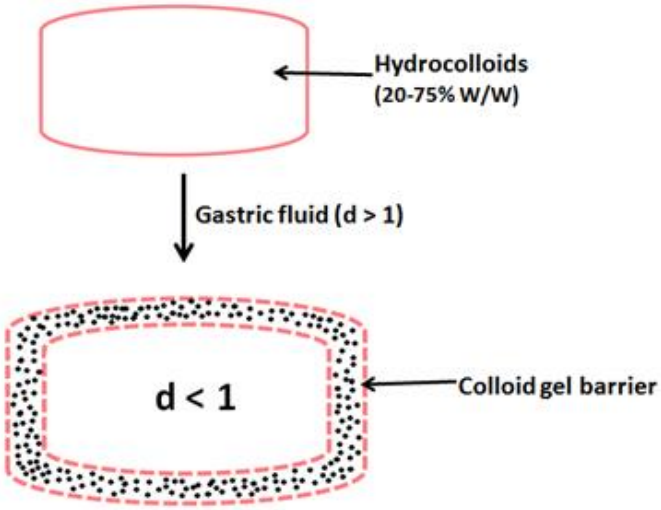

Figure 3: Intra gastric single layer floating tablet (US Patent #4, 167, 558, September 11, 1979).

stomach for a drawn out period. A thickness of < 1.0 gm/cm3 is required to display floating property[36].

Size and shape of the dosage form

Size and state of measurements unit likewise influence the gastric purging. In 2005 Garg and Sharma reported that tetrahedron-and ring-formed gadgets have a superior gastric residence time when contrasted and different shapes. The distance across of the measurement unit is additionally similarly imperative as a detailing parameter. Measurements shapes having a width of more than 7.5 mm demonstrates a superior gastric residence time contrasted and one having 9.9 mm.

Food intake and its nature

Nourishment intake, thickness and volume of sustenance, caloric worth and recurrence of sustaining profoundly affect the gastric maintenance of measurement structures. The nearness or nonappearance of sustenance in the gastrointestinal tract (GIT) impacts the gastric maintenance time (GRT) of the measurements structure. Typically the nearness of sustenance in the gastrointestinal tract (GIT) enhances the gastric maintenance time (GRT) of the measurements structure and along these lines, the medications ingestion increments by permitting its stay at the assimilation site for a more drawn out period. Once more, increment in corrosiveness and caloric quality shows diminish in gastric discharging time (GET), which will enhance the gastric maintenance of the measurements shapes[65].

Effect of gender, posture and age

For the most part females have slower gastric discharging rates than the male. The impact of stance does not have any critical distinction in the mean gastric maintenance time (GRT) for people in upright, mobile and recumbent state. In the event of elderly persons, gastric exhausting is backed off[66].

Sustained Release

Sustained release (SR) compositions were modified and new techniques were introduced. They are termed as "slow release" when compared to "rapid" or "conventional" release preparations. The terms consistently imbricate with controlled release, which signifies more practically control of release and not limited to the time dimension. The drug in controlled release preparation involves stability, while in the case of sustained release the drug is not consistent. The following are the reason for developing SR:

- Extending the time span of the drug
- Avoiding the number of dosing
- Reducing variations in plasma level
- Increasing drug utility
- Limiting the undesirable effect

Sustained release is the slow release of the drug over a period of time. It may or may not be a controlled release. It gives drug treatment over a prolonged period of time or signifies that the system is able to contribute some definite therapeutic control whether it is secular nature or spatial

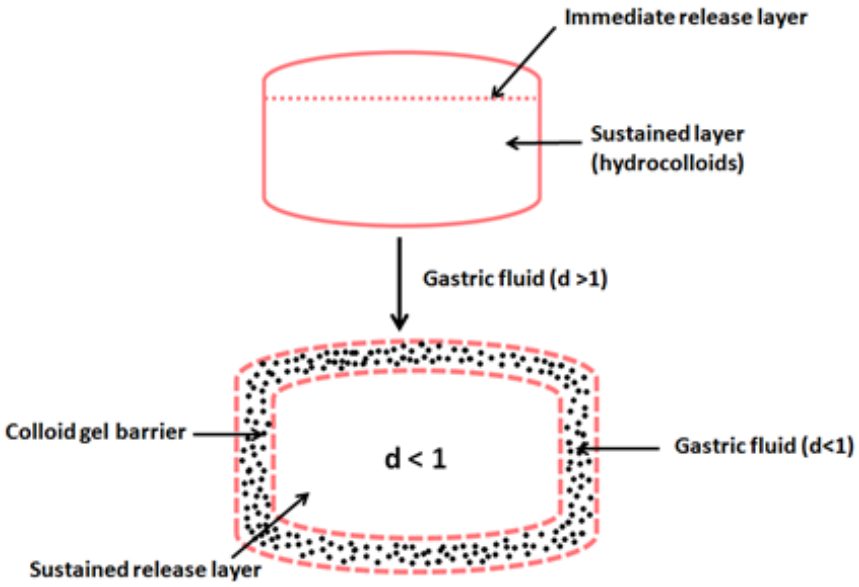

Figure 4: Intra gastric bilayer floating tablet (US Patent #4, 140, 755, February 20, 1979).

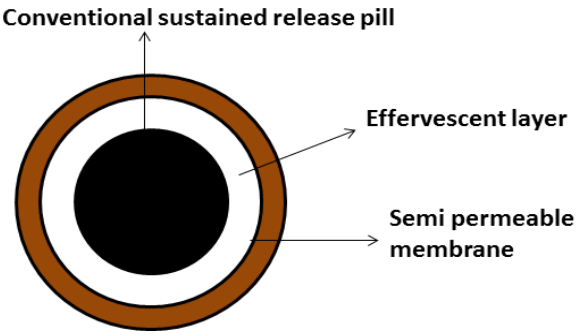

Figure 5: A multiple-unit oral floating dosage system (Amit Kumar Nayak et al, 2010).

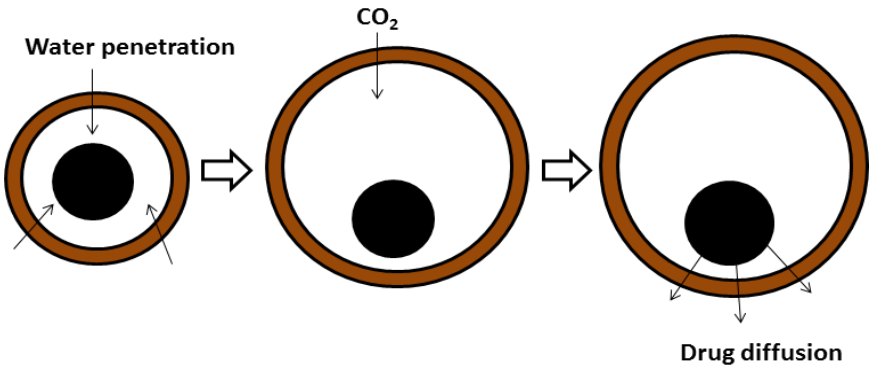

Figure 6: Drug release from effervescent systems (Shakti Dwivedi et al, 2011).

nature or it may be of both. Typically, this technology is called as Time Release Technology which includes sustained-release (SR), extended-release (ER, XR, or XL), time-release or timed-release, controlled-release (CR) and continuous-release (Contin). The tablets, pills or capsules are developed to dissolve slowly and release the drug over a prolonged period of time. The fundamental favourable circumstances of this maintained discharge tablets or cases is that they can regularly be taken less habitually than moment discharge plans of the same medication, and that they keep steadier levels of the medication in the circulatory system. Maintained discharge tablets are planned so that the dynamic fixing is implanted in a lattice of insoluble substance (different: a few acrylics, even chitin, these are regularly licensed) so that the dissolving drug needs to discover out through the gaps in the grid. In some SR plans the network physically swells up to frame a gel, so that the medication has first to break up in grid and afterward exit through the external surface[47,67-70].

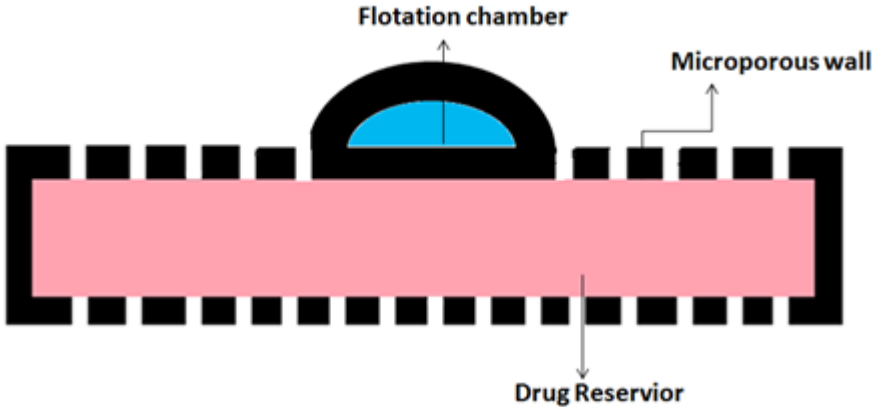

Figure 7: Intra gastric floating drug delivery device (US Patent # 4, 055, 178, October 25, 1977).

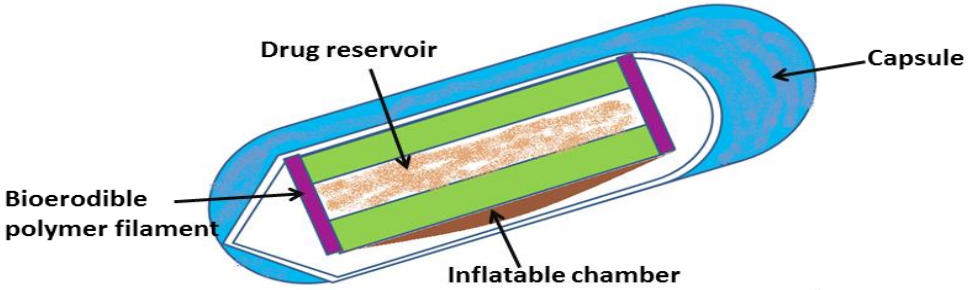

Figure 8: Gastro-inflatable drug delivery device (Debjit Bhowmik et al, 2009).

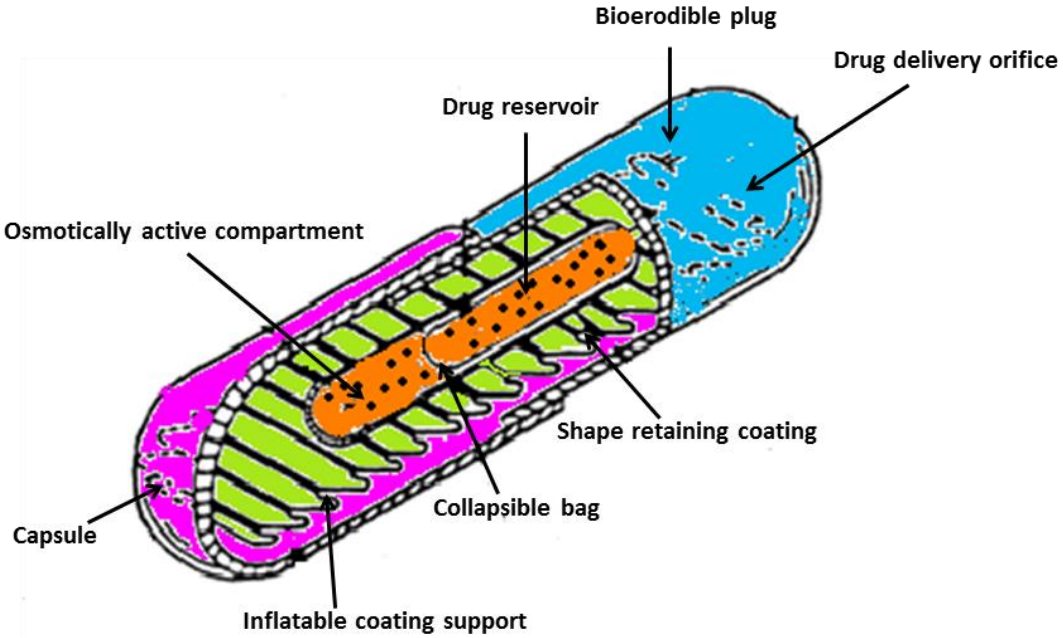

Figure 9: Intragastric osmotically controlled device (Brahma N. Singh, 2000).

There are certain considerations for the formation of sustained release formulation:

- If the dynamic compound has a long half-life (more than 6 hours), it is managed all alone.
- If the pharmacological movement of the dynamic compound is not identified with its blood levels, time discharging then has no reason.
- If the assimilation of the dynamic compound includes an active transport, the advancement of a time release product might be risky.
- Finally, if the dynamic compound has a short half-life, it would require a substantial add up to keep up a delayed viable dosage. For this situation, a wide restorative window is important to maintain a strategic distance from poisonous quality; generally, the danger is

ridiculous and another method of administration would be suggested.

CONCLUSIONS

The most sensible methodology for achieving a proceeded and anticipated medication release in the gastrointestinal tract is to control the gastric residense time utilizing gastro retentive measurements. To acheive this, the floating drug delivery system has turned out as a potential methodology for expanding the bioavailability and supported conveyance of different remedial particles. The expanding advancement of conveyance innovation will guarantee the improvement of expanded number of gastroretentive medication conveyance to streamline the delivery of molecules show absorption window, low bioavailability and broad first pass metabolism. FDDS is a kind of challenge and the work will continue endlessly until a perfect methodology with modern pertinence and attainability arrives .

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