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Gastroretentive Drug Delivery System: An Overview

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ABSTRACT:
One of the novel approaches is FDDS (floating drug delivery system). It is a subcategory of the gastroretentive drug delivery system. Floating drug delivery system discovered in 1968 byDavis^.The main approach of FDDS is to float dosage form in the gastric fluid to increase gastric residence time by using different pharmaceutical active pharmaceutical ingredients. FDDS is mainly used for poorly soluble drugs or have poor stability in the stomachic fluid. The excipients and pharmaceutical polymers used for gastro retentive delivery have bulk density lesser gastric fluid so that they provide needed buoyancy to float over gastric fluid for a great duration. The preferable route for administration of floating dosage form is the oral route as it is the easiest way to take medications.The review, in brief, describes the mechanism, forms of floating system, advantages, limitations, factors touching floating system, drug candidates appropriate for floating, analysis parameters and application of the system. These systems are helpful to many issues encountered throughout the event of a pharmaceutical dose type and therefore the futurepotential of FDDS.

Keywords: GRDDS, Sustained release, various approaches.

I. INTRODUCTION:

The oral route has been the most convenient and accepted route of drug delivery. We used to administer pharmaceutical dosage through the oral route as it is useful to upkeep an effective concentration in the system for a longer duration and also it helps provide easy dosage administration to the patient. From a pharmacokinetic point of view, the ideal sustained and controlled release dosage form should be comparable to an intravenous infusion, which supplies continuously the amount of drug needed to maintain constant plasma levels once the steady state is reached(3).

The Gastric retentive drug delivery system is one of the novel approaches in the drug delivery system. The main approach of GRDDS is to improvethe residence time of pharmaceutical dosage forms in the gastric environment. Dosage forms that return in the stomach are called GRDDSs. It is most beneficial in increasing the activity span for short half-life drugs. GRDDS refers to an increase in the extent to of pharmaceutical dosage forms become completely available to the systemic circulation. GRDDS is categorized into Bioadhesive system,floating system, non-floating system, swelling system,etc.However, this route has several physiological problems. Including an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time (8- 12h), and the existence of an absorption window in the upper small intestine for several drugs(9).A gastro retentive drug delivery system can improve the controlled delivery of drugs which has a narrow absorption window in the upper gastrointestinal part ofthe stomach (9).Gastric avoidance of dose forms is a particularlyvariable method and the skill to prolong and managethe voidance time may be a valuable plus for the doseforms, that reside within the abdomen for an extendedperiod of your time than typical dose forms.Gastric voidance happens throughout abstinence also as tofed states. The pattern of motility is distinct within the pair of states. throughout theabstinence state Associate in Nursinginter-digestive series of electrical events turn up,which the cycle each through the abdomen and viscusevery twoto three hours(3).This is referred to as the inter-digestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following four phases as delineated by Wilson and Washington(4,5)

1. Phase I (basal phase) lasts from forty to sixty minutes with rare contractions.

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2. Phase II (pre burst phase) lasts for forty to sixty minutes with intermittent impulses and contractions.

As the section progresses the intensity and frequency also will increase bit by bit.

3. Phase III (burst phase) lasts for four to six minutes. It includes intense and regular contractions for a short amount. Because of this wave, every one of the undigested material is swept out of the stomach all the way down to the tiny internal organ. It is also known as the domestic help wave.
4. Phase IV clinical trials last for zero to five minutes and happen between phases III and one of two consecutive CYCLES.

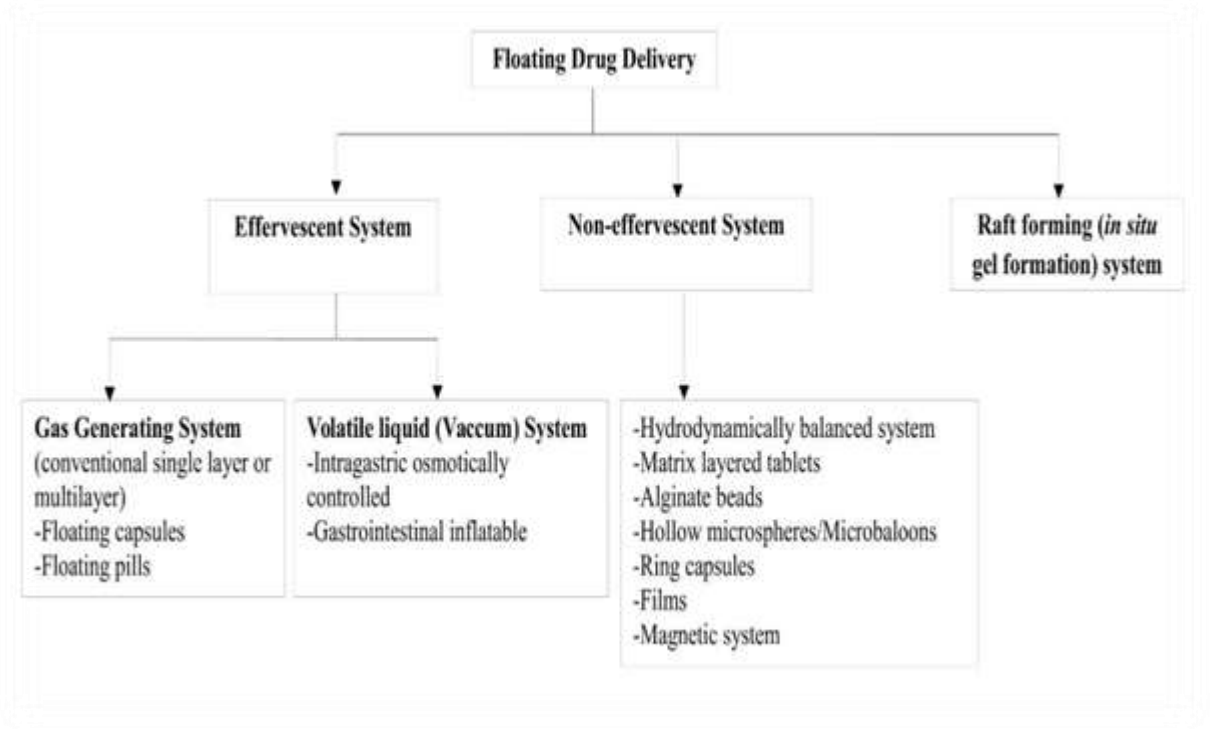
After the bodily process of a mixed meal, the pattern of contractions changes from fasted to it fed state. this is often additionally called biological process motility pattern and contains continuous contractions as in phase II of the fasted state. These contractions end in reducing the dimensions of food particles (to but one mm), that square measure propelled toward the porta in an exceedingly suspension kindthroughout the fed state onset of MMC is delayed leading to lag of stomachal emptying rate.(7)

Floating drug delivery systems:

Floating systems are denseness systems that have decent buoyancy to float over the stomachal contents and remain within the abdomen for a protracted amount. While the system floats over the stomachal contents, the drugis free slowly at the specified rate, which results in inflated gastro-retention time and
reduces fluctuation.

Classification of floating drug delivery systems (2).

Two distinctly different technologies have been utilized in the development of FDDS, according to the mechanism of buoyancy(1).



Classification of FDDS(26).

(A)Non-effervescent systems: this sort of system, once swallowing, swells via imbibition of stomachal fluid to associate extent that it prevents their exit from the abdomen. The formulation methods of such sort dose forms involve the mixing of thedrug with a gel, that swells when comes in-tuned with stomachal fluid and maintains relative integrity of form and a bulk density of but one among the outer gelatinous barrier. The air cornered by the swollen compound provides buoyancy in these dosage forms. the foremost usually used excipients in these systems embody hydroxypropyl alkyl radical polysaccharide (HPMC), polyacrylate polymers, vinyl polymer,

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Carbopol agar, metallic element alginate, calcium chloride, polythene compound, and polycarbonates. this method may be divided into four sub-types.(7)

(I) Colloid barrier system: These forms of systems contain drugs with gel-forming hydrocolloids which permit them to stay buoyant on the abdomen content. This prolongs GRT and maximizes the number of drugs at its absorption sites within the resolution form for prepared absorption. this method incorporates a high level of 1 or additional gel-forming extremely soluble polyose sort hydrocolloid as hydroxypropyl polyose, hydroxyethyl polyose. This substance hydrates and forms a mixture gel barrier
around its surface once returning connected with stomachal fluid and additionally helps in sustain releasing of the drug.

(II) Microporous Compartment system: during this technology, a drug reservoir is encapsulated inside a microporous compartment with pores along with its prime and bottom walls. The peripheral walls of the drug reservoir compartment area unit are fully sealed. This sealing prevents any direct contact of the stomachal surface with the un-dissolved drug. The flotation chamber contains the delivery system to float over the stomachal content entrapped air permits, within the abdomen. Gastric fluid enters through the associate aperture, dissolves the drug, and carries the dissolved drug for continuous transport across the gut for absorption.

(III) Alginate beads: To develop multi-unitfloating dose forms, the freeze-dried
calcium alginate has been used. Spherical beads of roughly two.5 metric linear units in diameter can be ready by the precipitation of calcium alginate via dropping atomic number 11 alginate answer into a solution of calcium chloride. The beads area unit than
separated, snap-frozen in cryogen, and freeze-dried at -40ºC for twenty-four hours, it results in the formation of a porous system that may maintain a floating force for over twelve hours. These floating beads prolonged residence time for over 5.5 hours.

(IV) Hollow Microspheres/Microballons: A novel emulsion solvent diffusion methodology used to prepare hollow microspheres loaded with the drug in their outer compound shelf ethanol/ methylene chloride answer of the drug and Associate in Nursing enteric acrylic compound was poured into Associate in Nursing agitated answer of polyvinyl alcohol (PVA) that was thermally controlled at 40ºC. The gas section is generated within the spread polymer driblet by the evaporation of dichloromethane shaped within the internal cavity of the microsphere of the compound and drug. The micro balloon floated unceasingly over the surface of Associate in Nursing acidic dissolution media containing a chemical agent for over 12h.

(B) Effervescent Systems: These buoyant systems utilize matrices ready with swellable polymers like methocel polysaccharides (e.g., chitosan) and effervescent parts (e.g., sodium hydrogen carbonate, acid, or salt acid). The system is therefore ready that once it arrives within the abdomen carbonic acid gas is released, inflicting the formulation to float within the stomach.

Advantages of Floating Drug Delivery:

1. Increased Bioavailability:The bioavailability of some medications (e.g. riboflavin and levodopa) CR-GRDF is considerably enhanced as compared to the administration of non-GRDF atomic number 24 compound formulations.
2. Increased First-Pass Biotransformation:When the drug is conferred to the metabolic enzymes (cytochrome P-450, above all CYP-3A4) in a sustained manner, the systemic metabolism of the tested compound is also significantly multiplied rather than by a bolus input.
3. Sustained drug delivery/reduced frequency of Dosing: The medicine hasa short biological half-life, a sustained and slow input from FDDS might lead to a flipflop Materia medica and it reduces the dose frequency. This feature isassociated with improved patient compliance and so improves medical aid.
4. Targeted medical aid for native ailments within the upper GIT: The prolonged and sustained administration of the drug from FDDS to the abdomen could also be helpful for native medical aid in the abdomen.
5. Reduced fluctuations of Drug concentration: The fluctuations in plasma drug concentration are decreased, and concentration-dependent adverse effects that are related to peak concentrations can be prevented. This feature is of special importance for medicine with a slender therapeutic index that produces it doable to obtain bound property within the induced pharmacological impact of medication that activates differing types of receptors at different concentrations.
6. Reduced counter-activity of the Body:Slow unleash of the drug into the body minimizes the counter activity resulting in higher drug potency.

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7. Extended time over important (effective) concentration: The sustained mode of administration permits an extension of the time
8. Improved Receptor activation selectivity:FDDS reduces the drug concentration fluctuation over an important concentration and thus enhances the medicine effects and improves the clinical outcomes.
9. Decreased adverse activity in the Colon:Retention of the drug in GRDF in the abdomen degradation of drug degraded within the colon.
10. Site-specificity Drug Delivery: A floating dosage kind could be a widely accepted approach, especially for medicine that has restricted absorption sites in the higher intestine.(10,12)

Limitations/Disadvantages:

i. These systems need a high level of fluid in the abdomen for drug delivery to float and work efficiently-coat.

ii. Not appropriate for medication that has solubility or stability downside in the bum.

iii. Medication like Procardia that is well absorbed on the whole bum and that
undergoes 1st pass metabolism, may not be desirable.

iv. medication that area unit annoyance to viscus mucous membrane is also not fascinating or appropriate.

v. The drug substances that are unit unstable within the acidic atmosphere of the abdomen aren't suitable candidates to be incorporated within the systems.

vi. The dose type ought to be administered with a full glass of water (200-250 ml).

vii. These systems don't supply important advantages over the traditional dose
forms for medication, that area unit absorbed throughout the canal(13,14,15).

MECHANISM OF FLOATING SYSTEMS

Floating drug delivery systems (FDDS) have bulk density lesser than internal organ fluids, so that they stay buoyant in the abdomen, while not touching the internal organ evacuation the rate for a protracted amount of your time. whereas the system is floating on the internal organ contents, the drug is free slowly at the specified rate from the system. However, besides the lowest internal organ content required to permit the

the proper accomplishment of the buoyancy retention principle, the lowest level of floating force (F) is additionally needed to keep the indefinite quantity type dependably buoyant on the surface of the meal. to live the floating force dynamics, a novel apparatus for determination of resultant weight has been reported within the literature. The equipment operates by measuring ceaselessly the force such as F (as afunction of time) that's needed to take care of the submerged object. This equipment helps in optimizing FDDS with regard to the stability and sturdiness of floating forces created to stop the drawbacks of unforeseeable intragastric buoyancy capability variations(16).

Evaluation Parameters Of Stomach Specific FDDS:

There area unit totally different studies reportedwithin the literature
indicate that pharmaceutical indefinite quantity forms exhibiting internal organ residence in vitro floating behaviour show prolonged internal organ residence in vivo. However, it has to be seen that smart in vitro floating behaviour alone isn't enough proof for economical gastric retention in vivo. the consequences of the simultaneous presence of food and the advanced motility of the abdomen area are unit tough to estimate. Only in vivo studies will give definite proof that prolonged internal organ residence is obtained.

1. **Measurement of buoyancy capabilities of the FDDS:**The floating behaviour was evaluated with resultant weight measurements. The experiment was carried out in 2 completely different media, deionised water so asto monitor doable distinction. The equipment and its mechanism area were units explained earlier in this article. The results showedthat higher relative molecular mass polymers with a slower rate of the association had enhanced floating behaviour and it had been determined more in simulated meal medium compared to deionized water.(18)
2. **Floating time and dissolution:**The check for floating time measuring is sometimes performed in aroused viscous fluid or zero.1 mole/ lit HCl maintained at 37°C. it's determined by victimization USPdissolution equipment containing 900 cc of 0.1mole/lit HCl because of the dissolution medium at 37°C. The time taken by the indefinite quantity type to float is termed floating lag time and also the time that the dosage type floats is termed the floating or flotation time.(19).A lot of relevant in-vitro dissolution methodologies are proposed to judge a floating drug delivery system (for pill indefinite quantity form)(20).A

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100 ml glass beaker was changed by adding a piece at the bottom of the beaker so that the beaker will hold 70 ml of 0.1 mol/lit HCl dissolution medium and allow an assortment of samples. A measuring instrument was mounted above the beaker to deliver the dissolution medium at a flow of two ml/min to mimic the viscus acid secretion rate. The performance of the changed dissolution equipment was compared with USP dissolution. equipment two (Paddle): the matter of adherence of the pill to the shaft of the paddle was ascertained with the USP dissolution equipment. The pill failed to keep on with the provoking device within the proposed dissolution methodology. The drug unharness followed zero-order dynamics within the planned method. The similarity of dissolution curves was observed between the USP methodology and therefore the proposed methodology at a 100% distinction level (f2=57). The proposed check might show smart in vitro-in vivocorrelation since an effort is formed to mimic the in vivo conditions like viscus volume, gastric emptying, and viscus acid secretion rate.(18)

3. **Drug release:**Dissolution tests are performed mistreatment of the dissolution equipment. Samples are withdrawn sporadically from the dissolution medium with replacement and then analysed for his or her drug content when associate degree appropriate dilution.
4. **Content uniformity, hardness, friability (for tablets):Drug loading, drug demurrer potency, particle size analysis, surface characterization (for floating microspheres and beads):**Drug loading is assessed by crushing an accurately weighed sample of beads or microspheres in a very mortar and supplementary to the acceptable dissolution medium that is then centrifuged, filtered and analysed by varied analytical ways like spectrophotometry. the share drug loading is calculated by dividing the number of drugs within the sample by the burden and simulated meal, total beads or microspheres. The particle size and also the size distribution of beads or microspheres area unitsare determined within the dry state exploitation of the optical research method. The external and cross-sectional morphology (surface characterization) is completed by scanning electron microscope (SEM)(21).
5. **Pharmacokinetic studies:** Pharmacokinetic studies arean integral part of the in vivo studies and several other works have been on it. The pharmacological medicine studies of calcium-channel blocker, from the loading pellets containing the drug, crammed into a capsule, and compared with the standard verapamil tablets of comparable dose (40 mg). The tmax and United Self-Defense Force of Colombia (0-infinity) values (3.75h and 364.65 ng/ml, respectively) for floating pellets were comparatively above those obtained for the conventional calcium-channel blocker tablets (tmax price one.21h, and United Self-Defense Force of Colombia price 224.22ng/mlh)(22).Not much distinction was found between the Cmax values of each of the formulations, suggesting the improved bioavailability of the floating pellets compared to the standard tablets. AN improvement in bioavailability has conjointly been determined with piroxicam in hollow polycarbonate microspheres administered in rabbits. The microspheres showed about 1.4 times additional bioavailability, and the elimination half-life was magnified by concerning 3 times more than the free drug.

Factors moving Floating Drug Delivery System:

a) **Density:**The density of the dose type ought to be less than the viscus contents (1.004gm/ml).

b) **Size and Shape:** dose type unit with a diameter of quite seven. 5-millimetre square measure reported having Associate in Nursing augmented GRT competed to with those with a diameter of nine.9 mm. The dose type with a form polyhedron and ring form devises with a flexural modulus of forty-eight and twenty-two. 5 kilo-pond per sq in (KSI) square measure reported having higher lowlife for ninety to 100% retention at twenty-four hours compared with different shapes.

c) **Fed or Unfed State:** underneath abstinence conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that happen every 1.5 to a pair of hours. The MMC sweeps undigested material from the abdomen and if the temporal arrangement of administration of the formulation coincides therewith with the MMC, the GRT of the unit may be expected to be terribly short. However, within the fed state, MMC is delayed and GRT is significantly longer.

d) **Nature of the Meal:** Feeding of indigestiblepolymers of carboxylic acid salts will amendment the motility pattern of the abdomen to a fed state, thus decreasing the viscus voidance rate and prolonging the drug unharness.

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e) **Caloric Content:** GRT may be augmented between four to ten hours with a meal that's high in proteins(23).

APPLICATION OF FDDS:

1. **Sustained drug delivery:**HBS systems will stay within the abdomen for long periods and therefore will unharness the drug over a prolonged amount of your time.The problem of short gastric continuance encountered with associate degree oral Cr formulation thence may be overcome with these systems(18).
2. **Site-specific delivery**: These systems are significantly advantageous for drugs that are specifically absorbed from the abdomen or the proximal part of the little bowel, e.g., (riboflavin and Lasix. Lasix is primarily absorbed from the abdomen followed by the duodenum. It's been rumoured that a monolithic floating dosage type with prolonged internal organ continuance was developed and also the bioavailability was increased.)AutodefensasUnidas de Colombia obtained with the floating tablets was approximately 1.8 times those of typical furosemide tablets(26,18,14).
3. **Maximize the bioavailability**:Gastro retentive floating drug delivery system is applied for extended the activity of the dose kind, drug to extended action bioavailability is maximized. (1,26)

II. CONCLUSION:

Gastro-retentive floating drug delivery systems have emerged as Associate in Nursing economical means of enhancing the bioavailability and controlled delivery of the manydrugs.The increasing sophistication of delivery technology can make sure the development of an increasing number of stomachic retentivedrug delivery to optimizethe delivery of molecules that exhibits absorption window, low bioavailability of intensive initial pass metabolism.

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