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FORMULATION AND EVALUATION OF GASTRO-RETENTIVE FLOATING MICRO-SPHERES: A SYSTEMATIC REVIEW

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ABSTRACT: Gastro-retentive drug delivery system is the novel controlled release system that overcomes the problem like the first-pass metabolism, narrow index of absorption, unstable in intestinal pH, low bioavailability. Different approaches to GRDDS are floating, muco-adhesive, swelling, high density, magnetic drug delivery system. The floating drug delivery system is the most promising approach. The dosage forms remain buoyant for a longer duration of time in the gastric fluid due to the low density of dosage form. Gastric residence time is increased. In this system, there is site-specific drug delivery in the upper part of GIT. Drug release is a slow and controlled manner; drug absorption is increased. The bioavailability of drug is enhanced. Floating microspheres are gaining attention because it remains buoyant for longer time and uniform distribution of drug over the gastric fluid. Fluctuation in plasma drug concentration is reduced. Gastro-retentive dosage form prolong dosing interval reduce the frequency of drug administration so increase in patient compliance. GRDDS is useful for sustained/controlled drug delivery. This article gives an overview of different gastro-retentive systems, suitable drug candidates for GRDDS, advantages, and disadvantages, factors affecting GRDDS, floating microspheres, methods of preparation, evaluation, and application. Also, this review includes different studies on floating microspheres by various researchers.

INTRODUCTION: The oral drug delivery system is the most preferable and easy route of administration. This is a highly acceptable route [1, 2, 3]. The oral route is the most convenient, and patient compliance is more. This route plays a major role in the controlled and sustained drug delivery system. Gastro retentive drug delivery system is one of the novels and controlled drug delivery systems.

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Gastro-retentive drug delivery system increases the bio-availability of drug substance as the drug remains in the stomach for longer duration, and drug release is for extended time. It also prolongs the dosing interval, so increase patient compliance.

Various innovative approaches of gastric retention include bio-adhesion, expansion system, high-density system, magnetic systems, super porous hydrogels, low-density system, raft forming system, floating ion exchange resins. The controlled drug delivery system is going to be retained in the stomach and is called a gastro-retentive drug delivery system (GRDDS). Many drugs have an absorption window from the stomach and proximal part of the small intestine. GRDDs

give a large absorption window for an extended period of time, and it leads to the achievement of optimum bioavailability. GRDDS is the system that has a dosage form of low bulk density than gastric fluid allows the dosage form to remain buoyant for a prolonged time. The floating system mainly contains tablets, pellets, microspheres, beads, matrix tablets, gelling suspension. In a multiple unit particulate system, drug is uniformly distributed throughout GIT.

Selection of Drug Candidates for GRDDS: [1]

- ✓ Drugs which are absorbed in stomach: *e.g.* Nizatidine [6], Piroxicam [7], Cefixime trihydrate [8].
- ✓ Drugs which are poorly soluble in alkaline pH.: *e.g.* Dipyridamole [9], Cimetidine [10].
- ✓ Drugs having a narrow absorption window: *e.g.*, Levodopa [11], Repaglinide [12], Furosemide [13].
- ✓ Drug degradation in the colon: *e.g.*, Nizatidine [6]
- ✓ Drugs that disturb normal colonic microbes: *e.g.* Antibiotics against *H. pylori*, Metronidazole [14].
- ✓ Drugs having rapid absorption in the GI tract: *e.g.*, Balofloxacin [15], Sumatriptan Succinate [16].
- ✓ Drugs having local action in the stomach: *e.g.*, Levofloxacin [17], Famotidine [18,] Roxatidine acetate HCl [19].
- ✓ Drugs which have low solubility at high pH: *e.g.* Dipyridamole [9], Cimetidine [10].
- ✓ Drugs that degrade in alkaline pH: *e.g.*, Cefpodoxime Proxetil [20], Valacyclovir HCl[21].

Drugs which are not suitable for GRDDS: [24, 27,29]

- Limited acid solubility: *e.g.*, Phenytoin.
- Instability in the gastric environment: *e.g.*, Erythromycin.
- For selective release in the colon: *e.g.*, 5 Amino Salicylic Acid and corticosteroids.

Advantages of GRDDS: [1, 26, 27, 28, 29] It reduces dosing frequency, therefore, increase in patient compliance, economic dosage forms and controlled delivery of drug and site-specific drug delivery.

- Bioavailability increases. Increase in efficiency. *e.g.*, Levodopa CR-GRDF than Levodopa non GRDF CR- polymeric formulation [11].
- ➢ It maintains a constant therapeutic effect for a prolonged period of time.
- ➢ Mucosal irritation of drugs decreases by slow and controlled release of drugs at a fixed rate. *e.g.*, NSAIDs- Ibuprofen [22], Ketoprofen [23].
- ➢ Effective in the treatment of *Helicobacter pylori* infection and GI disorder like Gastroesophageal reflux.
- ➢ Better effect for short half-life drugs, minimizing dosing frequency.
- ➢ Gastric irritation reduces by designing sustained release dosage forms.
- ➢ Dose dumping is less by floating drug delivery single unit system.
- ➢ Floating drug delivery systems convenient for drugs having limited absorption in the intestine, and for drugs that get absorbed from the stomach. *e.g.*, Antacids, ferrous salts.

Disadvantages of GRDDS: [1, 26, 29]

- ❖ Drugs which have stability and solubility problem in acidic pH cannot be used for GRDDS.
- ❖ Drugs which are irritant to gastric mucosa. NSAIDs and Aspirin cause gastric lesions.
- ❖ Floating drug delivery has some limitations like violent gas generation, the disintegration of dosage forms, burst release, dose dumping, and alkaline microenvironment.
- ❖ Drugs that have absorption throughout GIT are not beneficial for this system, *e.g.*, Isosorbide Dinitrate, Nifedipine [24].
- ❖ Variability in gastric emptying time and rate is a major disadvantage.
- ❖ Longer time for swelling in hydrogel based system.
- ❖ This system varies with the position of the person.

Factors to Be Considered for Development of GRDDS: [2, 26, 31, 33]

Density: Dosage forms having less density than gastric contents (1.004 g/L) have a tendency of floating drug delivery system.

Size: Dosage form size should be more than 7.5 mm and less than 9.5 mm, which shows gastric retention for a longer time.

Shape: FDDS retains in the stomach for a longer duration, gastric retention time dependent upon the shape of the dosage form. There were different shapes screened *in-vivo* for gastric retention potential. From these shapes, tetrahedrons (Each leg 2 cm long) and rings (3.6 cm in diameter) have been observed nearly 100% retention for 24 h [2].

Single or Multiple Unit: Multiple units shows more beneficial because of the foretell release profile.

Fed and Fasting State: Presence of food results in increase in gastric retention, which promotes dissolution of drug and results in greater residence time for the dosage form.

Nature of Meal: Gastric retention time of food like fat and protein are near 4-10 h.

Frequency of Food: GRT is increased 400 times with an increase in the frequency of food taken as compared to a single food.

Caloric Content: Fat promotes secretion of bile, and it results in increased gastric residence time. Protein diet increases gastric retention time about 4-10 h.

Approaches of Grdds: [4, 26, 27, 30, 31, 32, 35]

- High-density system.
- Expandable system.
- Floating system.
- Mucoadhesive system.
- Superporous hydrogels.
- Magnetic System.

1. High-density System: [1, 4] High-density system is one of the approaches of GRDDS. The dosage form contains more density than a normal system (~ 1.004 g/cm^3). In these formulations, there are the coating of some material like barium sulphate, zinc oxide, iron oxide, titanium dioxide. These systems have a density of about 3 g/cm^{3,} which is beneficial for gastric retention in rugae of the stomach and withstands peristaltic movement. Dosage form retains at about 2.6-2.8 g/cm^3 density at the lower part of the stomach, which is threshold density. This system has the drawback of scale-up to manufacturing when a high quantity of drugs (>50 %) is required to be used.

2. Expandable System: Expandable system is the approach of the gastro-retentive system. It has been formulated for the last 3 decades. Previously it was designed for veterinary purposes, but now it is widely used in humans too. It is an easy way to swallow the dosage form. The system gets expanded when the dosage form comes in contact with gastric fluid; it expanded to a larger size and released the drug for a longer duration. Gastric-retention of the expandable dosage form is increased by increasing the rigidity of the dosage form. Rigidized dosage form tolerates the peristalsis and mechanical contraction of the stomach.

3. Superporous Hydrogels: Superporous hydro-gels (Swellable System) are different from conventional hydrogels by post size and water absorption process [1]. Super porous hydrogels have average pore size >100 mm. Conventional dosage form has pore size 10 nm to 10 mm and slow water uptake and therefore requires more time to reach an equilibrium state. Super porous hydrogels are pH and temperature-sensitive. They have a high swelling capacity. In this system, croscarmellose sodium (AC-DI-SOL) is used as a composite material. Park *et al*., developed chitosan-based super porous hydrogels by freeze-drying method [38] Gupta and Shivkumar formulated Rosiglitazone and chitosan with glyoxal as cross-linking agent hydrogels by gas bowling method. Superporous hydrogels have high swelling capacity at acidic pH, so it is beneficial for gastro retentive delivery [39].

4. Magnetic system: The system uses magnetic energy for drug delivery [27]. The system contains magnet inside the core of the dosage form, and one another magnet is applied externally on the abdominal region. There is a problem of placing the magnet on the abdomen on the exact position. Urbina et al. formulated multiple controlled nanoparticles, which are magnetically and thermally controlled drug delivery. Magnetic controlled drug delivery prolongs the drug release on targeted site [40].

5. Mucoadhesive / Bioadhesive System: Mucoadhesive or bioadhesive is the system in which dosage forms adhere to the mucosal surface. This system contains polymer adheres to the epithelial surface in the stomach and enhances drug release. The prolonged gastric retention time up to 24 h may be achieved by mucoadhesive systems. The commonly used polymers for the development of Mucoadhesive are natural polymers (sodium alginate, guar gum, gelatine, *etc.*), Semi-synthetic polymers (Carbopol, HPMC, Sodium CMC). After oral administration of dosage form, it gets dissolved in gastric fluids, and sticks/ adheres to the mucosal surface. Mucoadhesion is by a different mechanism like wetting theory, electronic theory, adsorption theory, diffusion theory.

6. Floating System: The floating system is the low-density system. The dosage form remains buoyant on gastric fluid and drug releases slowly for a longer duration of time. It results in increased gastric residence.

Floating System is Classified: Non-effervescent system and Effervescent system

Effervescent System (Gas Generating System): [25, 26] There generation of CO_2 gas allows the dosage form to remain buoyant. The dosage form is developed by using swellable polymers like chitosan, methylcellulose. The most commonly used gas generating agents are sodium bicarbonate, citric acid, tartaric acid. When the developed dosage form (tablet) comes in contact with the gastric fluid and liberates CO_2.

Multiple Unit Type Floating Pills: This system contains sustained-release pills as seeds covered by double layer. The inner layer is an effervescent layer consists of tartaric acid, sodium bicarbonate. The outer layer is a swellable layer like shellac, PVA. When this system submerged by dissolution medium likes buffer solution at 37 ºC, pills get swollen, and density decreases to 1 g/mL. Thus the system gets floats because of the generation of CO_2. These systems start floating within 10 min and remain buoyant for 5-6 h. Another effervescent system contains a collapsible spring. Collapsible spring controls the release of drugs from the polymer matrix. This device contains body made up of non-digestible, acid-resistant, high-density polymer and a gelatine cap. At the lower end of the body there is orifice to control the release of the drug. In contact with water, gelatine cap and water-soluble tape get dissolved. There is a generation of CO_2 by the effervescent reaction between an acid (surrounding the spring) and bicarbonate ions. It results in floating of dosage form on the fluid.

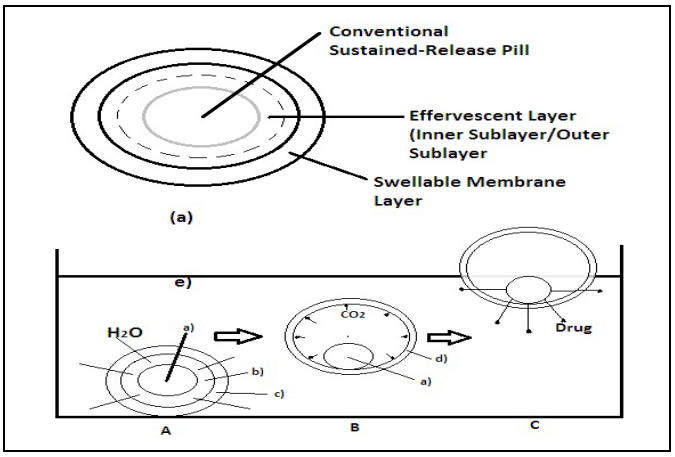

FIG. 1: MULTIPLE UNIT FLOATING SYSTEM: RELEASE OF CO_2

Non-Effervescent System: Non-effervescent system is based on the mechanism based on the bio adhesion of the mucous layer, swelling of polymers. In Non-effervescent system is gel-forming, and highly swellable polymers are cellulose hydrocolloids, polysaccharides hydrophilic gums, and matrix-forming material like polymethylacrylate, polycarbonate, polyacrylates and bioadhesive polymers like chitosan, alginate and guar gum.

Colloidal Gel Barrier System: It is a hydro-dynamically balanced system. The drug, along with the gel-forming hydrocolloids, tends to float on the gastric content, and it results in increased gastric residence. Such a system contains a high proportion of gel-forming agents and swellable polymers (25-75% w/w). Such a formulated matrix tablet or capsule in the presence of stomach fluid, hydrocolloid gets hydrated, and the colloidal gel barrier is developed at the solid liquid interface. Colloidal barrier controls the rate of delivery of the drug into bulk or GI fluid. Thus achieves the retardation effect/ sustain release of drug from the core.

Microporous Compartment System: [4, 27] In this system, drug reservoir is entrapped by microporous

compartment with opening at top and bottom walls. To prohibit any direct contact of the gastric mucosal surface with an undissolved drug, the drug reservoir is entirely sealed.

The system contains a flotation chamber with entrapped air, which float on the gastric content in the stomach. Gastric fluid enters through an orifice, the drug gets dissolved, and dissolved drugs continuously flow across the intestine for absorption. Floating carriers like hydroxypropyl cellulose, ethylcellulose, calcium silicate are used in intragastric floating and SR granules of diclofenac sodium [2].

Alginate Beads: Sodium alginate, calcium alginate, calcium chloride are used for the multiunit floating dosage form. Calcium alginate beads are formed by sodium alginate solution dropped into calcium chloride solution, cause precipitation of calcium alginate. Thus, alginate beads are formed. They are frozen in liquid nitrogen, and the porous system is formed after freeze-drying at -40 ºC for 24 h. Such floating microbeads gave longer gastric residence time more than 5.5 h. PVA is a water-soluble additive widely used as it gives permeability by its porous nature.

Microspheres: Microspheres are solid, spherical particles ranging in size from 1 to 1000 mm. In which drug molecules are dispersed in solution or in crystalline form. Microspheres made up of natural or synthetic polymers. Natural polymers like albumin, gelatine. Natural products include proteins, fats, starch, waxes, and synthetic polymers like polylactic acid and polyglycolic acid.

There are two types of microspheres one is solid, and the other is hollow microspheres. They differ by density. Hollow microspheres or floating micro-spheres have low density; therefore, it gets float on gastric fluid. Gastric retention time is enhanced. The drug is released in a controlled manner for a prolonged period of time.

Hollow Microspheres: This is the most promising floating drug delivery system. It is a multiple unit system and remains buoyant for a prolonged duration. There is a hollow space inside the microsphere. And the drug is coated outside by polymers. Generally used polymers are eudragit, cellulose acetate, acrylic, PVA.

Methods used for hollow micro balloons are solvent evaporation, emulsion-solvent diffusion. Drug release is modified by changing polymer concentration, polymer plasticizer ratio. The floating ability of this system depends upon the type of polymers, type of plasticizers, solvents, methods employed for formulation. In novel technique ethanol: dichloromethane solution of drug and acrylic polymer is used.

Method of Preparation of Gastro-retentive Floating Microspheres: [33, 34, 35, 36, 37] There are various methods of preparation of floating microspheres.

- Emulsion solvent evaporation technique.
- Emulsion solvent diffusion technique.
- Emulsion cross-linking technique.
- Multiple emulsion technique.
- Coacervation phase separation technique.
- Spray drying technique.
- Ionic gelation technique.

Emulsion Solvent Evaporation Technique: It is the most employed technique of obtaining controlled release microspheres. In this, the coating polymer is dissolved in an organic solvent, which is immiscible with the aqueous vehicle. The core material is dissolved or dispersed in a coating phase. This solution is added to an excess amount of aqueous phase containing an emulsifier, and this is agitated with a propeller-type agitator. The size and shape of microspheres depend upon the time, speed of agitation, concentration of emulsifier. Subsequently, an organic solvent is evaporated and the formation of solid polymeric microparticle entrapping the drug. For the solvent evaporation technique, two types of emulsions o/w and w/o.

Emulsion Solvent Diffusion Technique: In this method, drug and polymer are dissolved in an organic solvent like ethanol and dichloromethane. This solution added dropwise to the external aqueous phase containing surfactant. Mostly sodium lauryl sulphate is taken as a surfactant. The solution is stirred continuously on the propeller type agitator. The ethanol diffuses into an aqueous phase, and polymer precipitate around dichloromethane droplets. Subsequently, evaporation of entrapped dichloro-methane and cavity is formed inside the microspheres. By this

method, there is the formation of uniform sized hollow microspheres. High entrapment efficiency is achieved.

Emulsion Cross-Linking Technique: This method is useful for natural polymer-carriers. Natural polymers like gelatine, albumin, and chitosan. The natural polymers are dissolved or dispersed in the aqueous phase. Then non-aqueous phase is added into it. The drug is dissolved in natural polymer. For gelatine polymer pre-heating at 40 ºC for 1h is necessary to dissolve drug into it. The resultant solution is added dropwise into the oil phase containing surfactant. The oil phase is liquid paraffin or vegetable oil. This solution is stirred by triple-blade stirrer at a speed of 1000 rpm for 1 h.

Formed microspheres are filtered, washed by an organic solvent such as isopropyl alcohol, petroleum ether. Such microspheres are cross-linked by dispersing in cross-linking agents such as glutaraldehyde. The main disadvantage of this method is the exposure of the drug to chemical agents. The natural surfactants are added to stabilize the emulsion. The concentration of emulsifier influences the size, shape, surface morphology, entrapment efficiency, drug release.

Multiple Emulsion Technique: In this method, natural polymers like proteins, carbohydrates are prepared by primary emulsion o/w type. The drug is dissolved in water-soluble protein. An emulsifier is added to it. Then the dispersed organic phase added. This primary o/w emulsion is subjected to homogenization. Then an aqueous solution of polyvinyl alcohol poured into a primary emulsion. This is the formation of double emulsion w/o/w. This double emulsion is subjected to solvent evaporation or solvent extraction. And there is the formation of low density floating microspheres.

Coacervation Phase Separation Technique: In this technique, there are three steps; one core material is dispersed in the coating polymer solution. There is a formation of three immiscible layers. Second is the coating of polymer around core. Third is rigidization of coating polymer.Three immiscible phase influenced by different factors like, thermal change, non-solvent addition, incompatible polymer addition, salt addition, pH change. Rigidization of coating material by addition of cross-linking agent, thermal process, desolvation, using a non-aqueous vehicle, by salting out. By applying heat or using a solvent that can extract or remove solvent from coated microspheres.

Spray Drying Technique: It is the widely used technique in the industrial process for the formation of particles.

This polymer is added to a volatile organic solvent such as ethanol, acetone, and dichloromethane to form a slurry. Then the drug is dispersed in polymer solution under high-speed homogenization. Hot air atomization of the dispersion takes place. After a small atomization droplet or fine mist is formed. The solvent gets evaporated. Microspheres of size 1-100 mm formed. By the use of cyclone separator microspheres are separated by hot air.

Ionic Gelation Technique: This technique is successfully used for the preparation of floating microspheres. There is a cross-linking of polyelectrolyte in the presence of a counter ion to form a gel matrix. Polyelectrolyte, such as sodium alginate used. It coats the drug core and acts as a release retardant. It contains anions, which form a meshwork structure by combining with polyvalent cation. Drug and sodium alginate dispersion is dropped by needle into Calcium chloride solution. In this system, gas generating agents such as citric acid, tartaric acid added. The dispersion solution is stirred by a magnetic stirrer. Formed microspheres separated and collected. Natural polymer like sodium alginate improves entrapment efficiency.

Characterization of Gastro Retentive Dosage Forms: [2, 34, 35, 37] Characterization is performed to assure the performance of dosage form, quality control. Generally, for single unit dosage forms like tablet, capsules evaluated for weight variation, hardness, thickness, friability, percentage drug content, disintegration time, drug release. For GRDDS require specific tests for evaluation.

For Floating Microspheres:

Micromeritics, Particle size Characterization, Surface Topology, Drug Loading: Flow properties determined by bulk density, tap density, Carr's index, Hausner ratio. Particle size and surface topology are determined by optical microscope, SEM (Scanning electron microscope),

TEM (Transmission electron microscope). Drug entrapment efficiency or drug loading is analyzed by UV, HPLC.

Fourier Transform Infrared Analysis (FT-IR): FT-IR analysis detects the functional group of the organic, inorganic polymer. The pure drug, drug-polymers compatibility, drug-loaded compounds are determined by the FT-IR technique.

Thermal Analysis: Differential scanning calorimetry (DSC) is performed to characterize water of hydration of the compound. Pure drugs and drug-polymer formulations crystallization, fusion, and glass transition temperature are characterized. Cross-linking of polymers, exo-thermic processes are determined.

Buoyancy / Floating time: Buoyancy test is carried out in simulated gastric and intestinal fluids. Temperature is maintained at 37 ºC. 900 mL of 0.1 N HCl is a medium taken for this test. This test is performed by using the USP dissolution apparatus containing the dissolution medium at 37 ºC.

The time for which the dosage form remains buoyant is flotation time and time taken by dosage form to get float is floating lag time [35].

$$\text{Buoyancy percent} = W_f / (W_{f+} W_s) \times 100$$

Where W_f and W_s are weights of floating and settled microspheres, respectively.

Resultant Weight: It is the system that determines the real floating ability of the dosage form. It has an *in-vitro* measuring apparatus. This system measures force equivalent to F required to maintain the object totally submerged in the fluid. This force discovers the resultant weight of the object is immersed condition. This gives the floating capacity to the dosage form.

Swelling Studies: The known quantity of microspheres is soaked in 0.1 N HCl or 6.8 pH phosphate buffer at 37 ºC in a glass beaker for a required period of time. Allow swelling. Change in weight is observed.

***In-Vitro* Drug Release:** *In-vitro* Drug release study is carried out in a USP dissolution apparatus. Different types of dissolution apparatus used for different dosage forms.

The dissolution medium is simulated gastric fluid pH 1.2 at 37 ºC. Test samples are withdrawn for a particular time interval and analyzed on UV spectrometer, HPLC for drug content determination. *In-vitro* drug release data is evaluated by kinetic mathematical models like zero order, first order, Higuchi, Korsemayers Peppas models.

Entrapment Efficiency: Drug loaded in the microspheres is determined by dissolving a weighed amount of crushed microspheres in a sufficient quantity of 0.1 N HCl. That solution is analyzed by a UV spectrophotometer at a particular wavelength.

Entrapment efficiency = Practical amount of drug content / Total theoretical amount of drug content *100

Bioadhesive Strength: It is the strength required to detach from the biological surface. It is the measurement of force to get a separate polymer specimen between artificial or biological (rabbit stomach tissue) layers. By using a precision balance or automated texture analyzer, that force is measured.

Swelling System:

Water Uptake Study and Weight Gain: A swelling study of the dosage unit is done by measuring any dimensional study, water uptake, and weight gain. The dosage form is immersed in the simulated gastric fluid at 37 ºC. Change in a dimension like thickness, length, weight is observed at a regular time interval. There is an increase in tablet diameter, thickness with time. Water uptake is measured by weight gain. The Equation is:

$$WU = (Wt - Wo) *100 / Wo$$

Wt and Wo are weights of the dosage form at time t and initial time, respectively.

Gastroretention: It is the *in-vivo* parameter of evaluation, retention of the dosage form in the GI tract. In this technique, the radio-opaque material into solid dosage form is visualized under X-rays. The inclusion of gamma radionuclide in the dosage form enables indirect external observation using a gamma camera or scintiscanner. The dosage form position in the GIT is observed by this method. The gamma rays emitted by radio-nuclide caused by the

camera, which monitors the location of the dosage form in the GI tract.

Determination of Drug Content: Drug present in the dosage form should be within the specified limits. The actual quantity of drug present in the formulation is percent drug content. Drug content is measured by instruments like HPLC, HPTLC, UV methods.

Dissolution Study: A dissolution study is performed to determine the release of drug within the specified medium and time. USP dissolution apparatus is used to perform this test.

The different formulation requires a different type of apparatus. Mostly USP type II apparatus (Paddle) is used. Samples are withdrawn repeatedly from the dissolution medium and replaced by the same amount of dissolution medium, and the test is carried out to determine drug release. And by using the standard calibration equation, the cumulative percentage of drug release is calculated. Following **Table 1** gives the highlights for the various studies carried out by various researchers for the development of gastro-retentive microspheres with the outcome.

TABLE 1: VARIOUS STUDIES CARRIED OUT BY VARIOUS RESEARCHERS FOR THE DEVELOPMENT OF GASTRO-RETENTIVE MICROSPHERES WITH THE OUTCOME

Drug	Technique	Excipients Used	Outcome
Acebutolol	Solvent diffusion evaporation technique	Cellulose Acetate (F1), EdurgitS100 (F2), Acrycoat S100 (F3)	The microspheres prepared by Ethyl cellulose polymer shows more drug release and remain buoyant for 12 h [41]
Atazanavir sulphate	Double emulsion $w_1/o/w_2$ solvent evaporation	Eudragit E 100, HPMC, Ethylcellulose	Eudragit formulations showed an increase in entrapment efficiency because of large particle size and increased viscosity. HPMC and ethyl cellulose formulation have sustained release behavior [42]
Acyclovir	Solvent diffusion evaporation method	Ethylcellulose, Hydroxyl propyl methylcellulose, PVA	Microspheres formulations showed food floating ability and prolonged drug release which are suitable for intragastric multiple unit drug delivery [43]
Atenolol	Solvent diffusion method	HPMC, EC, Acetone ethanol, liquid paraffin, tween 80	Incorporation of the hydrophilic polymer HPMC in the shell of microspheres, the amount of drug release from microspheres could increase [44]
Amoxicillin Hydrochloride, Nizatidine hydrochloride,	Solvent evaporation method	Polymethyl methacrylate, Dichloromethane and Dimethylformamide	By increasing drug concentration, entrapment efficiency increased, on the further increased drug is gradual decreases. As the temperature increased, the average particle size decreased [45]
Balofloxacin	Solvent diffusion method	Ethylcellulose, HPMC K 4 M, Eudragit RSPO	Microspheres were discrete, spherical in shape, free-flowing. Observed *in-vitro* drug release is 80-98 % at the end of 12 h. Remain buoyant for more than 12 h.[15]
Capecitabine	o/w emulsification solvent evaporation method	Ethyl Cellulose, Tween 80	The formulation showed drug release and floating behavior up to 8 h. Drug release is first-order kinetics. By increasing, polymer content drug loading decreases [46]
Cefdinir	Solvent evaporation method	HPMC, Ethylcellulose and Eudragit, PVA	Microspheres of drugs with HPMC and Ethylcellulose were buoyant. Microspheres of Eudragit S 100 showed greater buoyancy (89%) percent yield (87.22%), drug entrapment efficiency (92 %) and highest *in-vitro* drug release 98.9 % within 12 h [47]
Cefixime trihydrate	Ionotropic gelation method	HPMC K4M, HPMC K15M,ethylcellulose, sodium alginate, calcium chloride, Sodium bicarbonate, Calcium carbonate	Drug entrapment efficiency decrease with the addition of a gas-forming agent. Microspheres containing Sodium bicarbonate were larger in size, and drug release was more. Microspheres containing calcium carbonate showed more buoyancy than sodium bicarbonate microspheres, and it does not change drug release behavior [8]
Cefpodoxime proxetil	Non-aqueous solvent evaporation method	HPMC K15, EC	Formulation containing a drug to polymer ratio 1:2 showed best drug release profile [20]
Dicycloverine hydrochloride	Ionotropic gelation method	Ethyl cellulose, PVP polyvinyl Pyrrolidine, HPMC, Calcium chloride.	Beads show improved oral bioavailability and prolonged release of drug [48]
Diltiazem	Non-aqueous	Polycarbonate, chitosan,	Formulation containing polycarbonate showed

hydrochloride	solvent evaporation	ethylcellulose, hydroxyl propyl methyl cellulose and acrycoat	maximum *in-vitro* drug release of 98.72% in 12 h [49]
Entacapone	Ionotropic gelation	Sodium alginate, HPMC K4M, Sodium bicarbonate, Calcium chloride	Drug release of microspheres followed zero-order and Higuchi model. Formulation F14 showed drug release for 12 h about 97.99 % [50]
Etodolac	Emulsion solvent diffusion evaporation	Eudragit RS 100, ethylcellulose	Formulation containing ethylcellulose: Eudragit RS 100 in 1:2 ratios showed good entrapment efficiency and drug release for 12 h (sustained-release) [51]
Esomeprazole magnesium trihydrate	Solvent evaporation method	HPMC, CA, Carbopol 940, Eudragit L 100	Percentage buoyancy and particle size was increased with the amount of polymer concentration [52]
Famotidine	Modified emulsion solvent diffusion technique	Hydroxypropyl methylcellulose, Ethylcellulose and Calcium silicate, PVA	Drug release decreased with an increase in ethyl cellulose. HPMC: EC at ratio 1:2 showed good microspheres [18]
Furosemide	Solvent evaporation method; Sustained release	EC,HPMC, sodium hydroxide and Tween 80, dichloromethane, hydrochloric acid	The yield of microspheres production was good with an increase in EC: HPMC ratio and at lower temperatures. Drug release more than 12 h and exhibit buoyancy for 12 h [13]
Piroxicam	Ionotropic gelation method	Sodium alginate, HPMC, Xanthan gum	As polymer concentration increases, particle size increases. Floating time increases with an increase in particle size. Microspheres remained buoyant for 12 h [7]
Hydrochlorothiazide	Orifice Ionic Gelation	Sodium alginate, sodium bicarbonate (gas generating), calcium chloride (cross-linking agent)	Particle size and entrapment efficiency increase with concentration. The drug release was decreased with an increase in polymer ratio. Formulation of the drug: polymer ratio as 1:3 was selected to be optimum for better entrapment [53]
Ibuprofen	Solvent evaporation method	Ethylcellulose, cyclohexane, tween 80, dichloromethane	Particle size, percentage yield, incorporation efficiency and drug release influenced by the increase in the concentration of tween 80 [22]
Ketoprofen	Solvent evaporation method	HPMC, Ethylcellulose, ,tween-80	Increased concentration of polymer, the viscosity increased, affecting stirring speed; therefore percentage yield decreased. Ketoprofen microspheres showed a reduction in gastric bleeding [23]
Levofloxacin	Solvent evaporation method	Eudragit S100, Eudragit L100, HPMC, Ethylcellulose, Ethanol & Dichloromethane	Ethylcellulose and Eudragit increased Gastric retention time and drug release for 12 h [17]
Lopinavir	Ionic gelation method	Sodium alginate, Calcium chloride	Microsphere size, drug release depends upon the drug polymer ratio. Sodium alginate showed good floating microspheres [54]
Losartan potassium	Solvent evaporation method	Sodium Alginate, HPMC K 100 , Tween 80	Drug entrapment efficiency slightly decreased with increase HPMC K100 concentration in microspheres. Formulations showed sustained release action for 24 h [55]
Lafutidine	solvent evaporation technique	HPMC K 15, Ethylcellulose, Eudragit® S 100, Eudragit® L 100	As the concentration of ethyl cellulose increased, and HPMC decreases, percentage yield increased. Stirring speed was increases and particle size was decreased [56]
Metformin hydrochloride	Solvent evaporation method	Eudragit RS-100 and RL-100	Gastric retention time increased oral bioavailability enhanced. Microspheres remained buoyant for 12 h [57]
Metformin hydrochloride	Emulsion solvent evaporation	Cellulose acetate, HPMC, Hydrochloric acid, Acetone, Span 80, Petroleum ether and Calcium chloride	Oral controlled release formulation, enhanced bioavailability [58]
Mebendazole	Solvent diffusion evaporation method	Ethylcellulose, hydroxyl propyl methylcellulose	Microspheres remained buoyant for 10 h. Floating behavior depends upon the nature of the polymer. Drug release showed first-order kinetics [59]
Metoclopramide hydrochloride	Non-aqueous emulsion solvent evaporation technique	Eudragit S100 (ES100), Eudragit L100 (EL100), Eudragit RS 100 (ERS100), Eudragit RL 100 (ERL100) and Ethylcellulose, Span 80, Tween 80	Increase in stirring rate decrease in particle size. By increasing drug concentration encapsulation efficiency increases but on further increase it gets decreases. As polymer concentration was increased in a formulation, drug release decreased [60]

Metronidazole	Ionic gelation method	cassava starch (*Manihot esculenta)*, sodium alginate, Calcium chloride, Sodium bicarbonate, zinc chloride	Controlled release formulation for 18 h. Swelling, buoyancy behavior depends upon the concentration of Cassava starch. Cassava starch showed shorter floating lag time and faster drug release [61]
Nateglinide	Oil-in-water emulsion solvent evaporation technique	Ethylcellulose, Eudragit S-100, ethanol, dichloromethane, tween-80	The formulated microspheres showed prolonged drug release of 12 h and remain buoyant for more than 12 h [62]
Nizatidine hydrochloride	Solvent evaporation method	Polymethyl methacrylate (PMMA), Dimethylformamide, Dichloromethane	By increasing the concentration of polymer entrapment efficiency increases, and on further increase in polymer entrapment efficiency decreases. As temperature increases, the particle size of formulation decreases [6]
Pantoprazole sodium	Solvent evaporation Method	HPMC K15M, ethylcellulose	Concentration of polymer ethyl Cellulose increases it influence the particle size, percentage yield, *in-vitro* buoyancy and drug release of the microsphere; formulation F6 showed Zero-order diffusion kinetics [63]
Ranolazine hydrochloride	Emulsion solvent diffusion evaporation	Sodium alginate, HPMC, Eudragit	Formulation containing Eudragit showed higher entrapment efficiency and buoyancy than HPMC & sodium alginate formulations [64]
Roxatidine acetate HCl	Emulsion Solvent Diffusion Technique	Ethylcellulose, Hydroxypropyl methylcellulose (HPMC K4M,HPMC K15M)	Microspheres containing more concentration of ethyl cellulose exhibited more buoyancy. As polymer concentration increases, viscosity increases, and entrapment efficiency increases. Formulation containing HPMC K4M: Ethylcellulose (1:2) showed good floating and drug release behavior [19]
Repaglinide	Solvent diffusion-evaporation Technique	Ethylcellulose (EC), polyvinyl alcohol (PVA) emulsifier, Analytical grade ethanol, dichloromethane	Desired microspheres showed drug release for 12 h. Floatability in gastric juice for a prolonged time [12]
Ritonavir	Emulsion solvent diffusion method	Eudragit L100, HPMC, ethanol, dichloromethane, PVA	Formulation FM1 prepared with polymer HPMC exhibited highest drug release (89.07 %) in 12 h. Stable for three months at ambient conditions, good buoyancy and prolonged drug release for 12 h [65]
Ropinirole HCl	Ionic gelation method	Sodium alginate, HPMC K15, Guar gum, Sodium bicarbonate, calcium chloride	Drug release was for 12h. Drug release showed zero-order and Higuchi model. Mechanism of drug release was diffusion controlled. Sustained-release behavior improves bioavailability [66]
Telmisartan	Non aqueous solvent evaporation method	kollidon SR, PEG 4000, Light liquid paraffin (LLP), Span 80	Kollidon SR can be successfully used to prepare floating microspheres to increase its gastric residence time and bioavailability [67]
Sumatriptan succinate	Ionotropic gelation technique	Sodium alginate, HPMC K4M,guar gum,	Sodium alginate and HPMC K4M shows higher drug release than other formulations. Sodium alginate alone does not sustain drug release [16]
5-Fluorouracil	Solvent diffusion–evaporation method	Span 80 concentration, ether/ethanol volume ratio, an polyvinyl pyrrolidone /ethylcellulose weight ratio	5-FU hollow microspheres possessed an excellent floating effect; 5-FU hollow microspheres showed significantly enhanced absorption and oral bioavailability with prolonging drug residence time [68]
1,1-Dimethylbiguanide	Ionotropic gelation technique	Sodium CMC, HPMC K 100 M, Sodium alginate, calcium chloride	Drug release is for 12 h. As polymer concentration increases, the drug release decreases. Formulations follow zero-order drug release [69]
Valacyclovir hydrochloride	W/O emulsification solvent evaporation method	Ethylcellulose (EC), dichloromethane: ethanol (1:1)., light liquid paraffin	Floating microspheres localize the drug at the upper part of GIT, for improved absorption and oral bioavailability *In- vitro*, floatability studies showed that 90 % of the microspheres were floated for more than 12 h [21]
Venlafaxine hydrochloride	Non-aqueous solvent evaporation	Ethylcellulose, Pullulan gum, dichloromethane ethanol, Tween 80, Liquid paraffin	Microspheres showed buoyancy more than 12 h. Drug release mechanism showed Fickian diffusion and swelling [70]

CONCLUSION: GRDDS system includes mainly floating, mucoadhesive, swelling system. These systems contain different dosage forms which enhance the bioavailability of the drug.

It is useful for sustained and controlled delivery of the drug in a site-specific manner. It prolongs the gastric retention time, thus increases therapeutic effectiveness. This system is suitable for the absorption of the drug through the upper part of GIT. It is suitable for the drugs which are prone to degradation in an acidic environment and less soluble in alkaline pH. GRDDS result in increased bioavailability for drugs.

Thus, it improves bioavailability. The system is also applicable for site-specific drug delivery as for *H. pylory* infection. Better for drugs that have a short half-life; thus, the dosing frequency is reduced and an increase in patient compliance. For designing of GRDDS dosage form, physic-chemical properties of drug, physiological event of GIT, and formulation strategy is important.

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