IJPSR (2021), Volume 12, Issue 6 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 27 April 2020; received in revised form, 02 May 2021; accepted, 11 May 2021; published 01 June 2021

FLOATING MICROSPHERES: A NOVEL EMERGING TREND IN GASTRO RETENTIVE DRUG DELIVERY

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Keywords:

Floating microspheres, GRDDS, FDDS, GRT

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ABSTRACT: Oral Conventional dosage forms offer no control over the release of drug from the dosage form, which leads to variations in plasma drug levels; gastric emptying and gastric resident time are two another important factors that have a significant effect on the therapeutic efficacy of drug and it causes changes in the retention time of the drug. Accordingly, Floating microspheres is one of the most dependable and inventive techniques among all the gastro retentive drug delivery systems to overcome from these problems. Floating microspheres are mainly obtaining importance because of their vast suitability in the targeting of drugs to the stomach, undergo action and scattered uniformly over the gastric fluid to avoid the changes of gastric emptying and enlarge the liberation of the drug. This system also allows vastly in the fabrication of new controlled and delayed-release oral formulations, thus Expanding revolutions in pharmaceutical Expansion. The present review, in brief, says the physiology of the Intestinal gastric tract and elements governs the gastro retentive drug delivery system. This review aims to illuminate the recent literature like the importance of floating microspheres in the Novel drug delivery system, methods of preparation, differentiation of Floating microspheres, and recent scientific advances in formulating floating microspheres using different classes of drugs.

INTRODUCTION: Floating drug delivery systems (FDDS) or hydro-dynamically balanced systems is a type of Gastro retentive drug delivery system that possesses a bulk density lesser than gastric fluids and remains floating in the stomach without arousing the effect of gastric-emptying rate for a longer period.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(6).3019-33

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(6).3019-33

The drug is slowly liberated at a desired rate from the floating system, and after the total release, the remaining materials of the dosage form is deported from the stomach. This leads to an improvement in the GRT and better control over changes in plasma drug concentration.

Thorough understanding connected with GI dynamics such as gastric emptying, small intestine transit, colonic transit, etc., is the way for the designing of oral controlled release dosage forms. The amount and magnitude of drug absorption from single areas of GI tract and elements that direct the absorption help for the preparation of dosage form [1].

The method of floating drug delivery has a bulk thickness of less than GI fluid and therefore lasts for a prolonged duration of buoyancy in the abdomen without impacting the rate of gastric emptying. The material floats in this process, and then it is delayed to release the material from the system at the critical rate after the release of the drug. This raises the risk of bacterial invasion of the body and results in good control of bacterial drug concentrations [2].

TABLE 1: ADVANTAGES OF CONVENTIONAL V/S GASTRO RETENTIVE DRUG DELIVERY SYSTEM [3]

Conventional	Gastro retentive drug delivery system
Not much Preferable for	Very much Preferable for
Drugs that are poorly soluble at an alkaline P_H	Drugs having rapid absorption through
Drugs acting locally in the stomach.	GIT
Drugs which degrade in the colon.	Drugs that degrade in the colon.
Drugs having rapid absorption through GIT	Drugs acting locally in the stomach
Inadequate for delivery of drugs with	Alternate for delivery of drugs with
definite absorption window in the small intestinal region	narrow absorption window in small intestinal region
Less patient compliance	More patient compliance

Advantages of Floating Microspheres: 4

- Enhanced bioavailability
- Enhanced first-pass biotransformation
- Sustained drug delivery/reduced frequency of dosing
- Targeted therapy for local ailments in the upper GIT
- Reduced fluctuations of drug concentration
- Improved receptor activation selectivity
- Reduced counter-activity of the body
- Extended time over critical (effective) concentration
- Minimized adverse activity at the colon
- Site-specific drug delivery
- Less inter-and intra-subject variability.
- Minimizes the counter activity of the body leading to higher drug efficiency.
- Fluctuations in drug concentration are minimized. Therefore, concentration-dependent adverse effects can be reduced.
- Sustained mode of drug release enables the extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.
- Flexibility in dosage form design.

Limitations: [5]

- Drugs that cause ulcers and irritation to gastric mucosa are not applicable for this delivery system.
- Drugs which are metabolized by the first-pass effect are not applicable for this type of drug delivery system
- Drugs which build solubility and stability problems in the gastric fluid are not suitable for this delivery system.

Basic Gastrointestinal Tract Physiology: Anatomically, the stomach is split into three areas like Fundus, body, and antrum. The proximal part made of fundus and body acts as a pool for undigested substance, antrum is the main site for blending motions and work as a pump for gastric emptying, complete propelling movement. Gastric emptying takes place during fasting as well as in fed states. The pattern of motility can be understood in the two states. During the fasting state, an inner digestive series of electrical events take place, cycling through both the stomach and intestine every two to three hours which is called as migrating myloelectric cycle (MMC) or inter-digestive myloelectric cycle, which can be further divided into four phases [6].

1. Phase I (basal phase): It continues from 40 to 60 min with unusual constrictions.

2. Phase II (preburst phase): It continuous for 40 to 60 minutes with period action potential and

constrictions. As this Phase is completed, the regularity and magnitude also rise progressively.

3. Phase III (burst phase): It is also known as the housekeeper wave. It continuous for 4-6 min. It contains severe and Systematic contractions for ales Period of time. Due to this wave, all the undigested material is wiped out of the stomach into the small intestine.

4. Phase IV: This is also called a digestive motility pattern and comprises continuous contractions as in phase II of the fasted state. It continuous for 0 to 5 min and occurs between phases III and I of two successive cycles.

Following the intake of a mixed meal, types of contractions change from fasted to a fed state. The contractions lead to reduce in the size of food particles to less than 1 mm, which are then pushed towards the pylorus in a suspension form. During the fed state, the onset of MMC is slowed, which leads to delaying of gastric emptying rate.

Scintigraphy studies have revealed that orally administered controlled-release dosage forms are subject to basically two complications, like inconsistent gastric emptying rate and shorter gastric residence time. Other different methods have also revealed the gap imbalance in gastric emptying in humans under normal gravity conditions are ultrasound, gastric aspiration, Magnetic resonance imaging (MRI) techniques, Epigastric impedance, Pellet Gastric Emptying Test (PGET), and Octanoic acid breath test.

Factors Affecting Gastro-retentive Drug Delivery: [7]

Fed or Unfed State (under fasting conditions): The appearance and Non-appearance of food directs the gastric retention time, normally the fed state upgrades the gastric retention time and elevates the absorption of the drug by extending the drug to last at the site of the absorption. In the fasting state, the GI motility is decorated by strong motor activity, which pushes the undigested material from the stomach to the intestine, and hence GRT is very small.

Frequency of feed: The GRT increases when meals are taken successively than a single meal, increases the GRT over 400 min.

Caloric and Nature of Meal: High caloric foods like proteins and fats increase the GRT from 4 to 10 h. Food carrying fatty acid salts or indigestible polymers can influence the motility pattern of the stomach which leads to reduce in gastric emptying rate and thus elongated the release of the drug.

Effect of Age, Gender and Posture: People with age above seventy have long GRT.GRT in females is less compared to males. The GRT is not affected due to posture, no significant difference in the upright and horizontal position.

Density of the Dosage Form: Density is significant factor that affects gastric emptying time and controls the buoyancy of dosage form. Mostly, dosage form with a density less than 1.0 gm/cm3 is ideal for showing good floating property.

Size of the Dosage Form: The giant size of the dosage form may not assign rapid movement through the pyloric antrum into the intestine. The residence time of Non-floating and floating dosage forms depends on the size of the dosage form. To pass from pylorus to intestine, the dosage must be in size range of 1- 2 mm. Dosage forms containing a diameter of more than 7.5 mm show a better gastric residence time when compared with dosage forms containing size 9.9 mm.

Shape of Dosage Form: Shape is a significant factor to plan a floating drug delivery system, tetrahedron, and ring-shaped devices with a flexural modulus of 48 and 22.5-kilo pounds per square inch (KSI) are established to have better gastric retention time up to 24 hours.

Concomitant Drug Administration: Prokinetic agents like Metoclopramide and Cisapride reduce gastric retention. Anti-cholinergic like Propantheline, Atropine, and Opiates like Codeine enhances gastric retention.

Physiological Factors:

Mechanism of Absorption: Drugs that are taken orally absorbed both by passive diffusion and non-passive absorption. Drugs absorbed by active and facilitated transport systems exhibit higher regional specificity due to the similarity of these mechanisms only in a peculiar area of the gastro intestinal tract.

Metabolic Enzymes: Enzymes present in a specific location in G.I. tract also lead to regional changes in absorption. Intestinal epithelium encloses phase-I metabolizing enzymes like cytochrome P-450, their action reduces longitudinally along the small intestine, and their levels are increasing from the duodenum to the jejunum and then reducing in the ileum and colon. This intermittent deposition of cytochrome P-450 makes variability's in the absorption of drugs that are substrate to this enzyme.

Mechanism of Floatation: To enhance the gastric retention time in the stomach various methods are used. The Floating drug delivery systems (FDDS) have every time lesser bulk density than gastric fluid and so encounter floatable in the stomach without showing any effect on the gastric emptying rate for a prolonged period. This set-up is floating on the stomach contents the drug is released slowly at the seek rate from the system. The apparatus handle by constantly computing the force equivalent to F (a function of time) that is used to maintain the submerged object. This apparatus helps in adjusting the floating drug delivery system concerning inflexibility and resilience of floating effect prompted in order to avert the disadvantage of unforeseeable propensity to float potentiality variability [8, 9].

$$F = F \text{ buoyancy} - F \text{ gravity} = (Df - Ds)\, gv$$

Where, F = total vertical force, D_f = fluid density, Ds = Object density, v = volume and g = acceleration due to gravity.

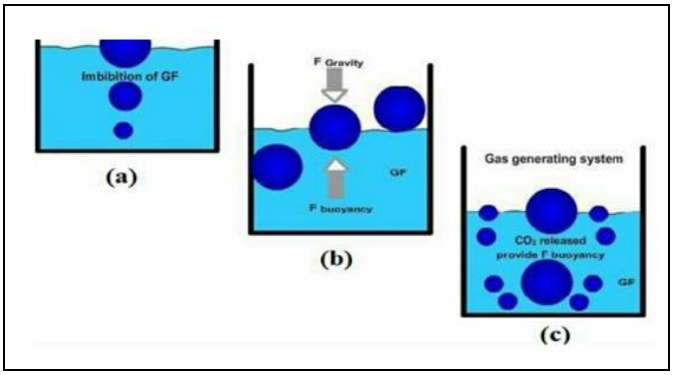

FIG. 1: MECHANISM OF FLOATING MICROSPHERE

Polymers used in Floating Microspheres: Microspheres can be formulated by taking both hydrophilic and hydrophobic polymers. Both biodegradable and non-biodegradable Polymers have been using for the manufacture of microspheres, and these involve polymers of natural, semi-synthetic, and synthetic origin [8].

Hydrophilic Polymers: Gelatine, agar, Egg albumin, starch, Chitosan, Cellulose derivatives; HPMC are the hydrophilic polymers used for manufacturing microspheres.

Hydrophobic Polymers: Ethylcellulose, Polylactic acid, PMMA, acrylic acid esters etc., are the hydrophobic polymers used for manufacturing microspheres.

Biodegradable polymers: These polymers disappear slowly from the site of administration; anyhow, due to hydrolysis, it appears as a reaction. Biodegradable polymers used are Polylactic acid (PLA), polyglycolic acid (PGA), Polycaprolactone (PCL) and many generic classes such as poly anhydrides and Polyorthoesters.

Non-Biodegradable Hydrophobic Polymers: These dormant are inert in the place of use and are abolished or originated from the region of administration. Non-Biodegradable Hydrophobic Polymers used for preparing microspheres are Ethylcellulose (EC), Cellulose acetate (CA), Polyethylene vinyl acetate (PEVA), Polyether urethane (PEU), Polyethylene (PE), Polydimethyl siloxane (PDS), and Polyvinyl chloride (PVC), Acrycoat, Eudragit S, *etc.*

Hydro Gels: These polymers tuff but do not melt when gets in contact with water. Hydrogels are dormant, unstayed from the site of administration, and acts by forming a rate limiting barrier to the transport and release of drugs. The hydrogels that are used for preparing microspheres are cross-linked Polyvinyl alcohol (PVA), Poly acrylamide, Poly hydroxyethyl methyl acrylate (PHEMA), Cross-linked Polyvinyl pyrrolidone (PVP), *etc.*

Soluble Polymers: These are with molecular weight (less than 75,000 Daltons) uncrosslinked polymer melt in water. The rate of dissolution weakened with elevating molecular weight. These polymers can be used alone or in combination with hydrophobic polymers so that the device slowly destroys over time. The soluble polymers taken for preparing microspheres are co-polymers of Meth acrylic acid and Acrylic acid methyl ester (Eudragit

L), Polyethylene glycol (PEG), Polyvinyl pyrrolidone or uncrosslinked polyvinyl alcohol, hydroxyl propyl methyl cellulose (Methocel).

Developmental Approaches for Floating Microspheres: A large number of fabrication methods available for the formulation of gastro retentive floating microspheres. But Emulsion solvent evaporation technique and Ion tropic gelation method has been greatly used by a number of methodical investigators to research the various perspective of floating microspheres. During the fabrication of floating controlled release microspheres, the use of the best technique is taken for the thorough entrapment of active ingredients. Choice of this method trusts upon the API and its planned use, nature of the polymer. Characteristic attributes of materials and the process taken greatly influence the formulated microspheres properties and also the controlled release rate from the dosage form.

1. Solvent Evaporation Method: To create the entire internal center through solvent diffusion and evaporation methods floating multi particulate dosage shape may be prepared. In a natural solvent, the polymer is dissolved, and within the polymer solution, the drug is either dispersed or dissolved. Then it emulsified containing suitable additive (surfactants/polymer) into an aqueous segment to shape o/w emulsion. The natural solvent is evaporated after the formation of a strong emulsion either through non-forestall stirring or developing the temperature below pressure. After solvent removal at the o/w interface of droplets, polymer precipitation occurs, and to impart the floating homes, hollow space develops. For the development of such systems, the polymers studied are cellulose acetate, polyethylene oxide, Eudragit, acrycoat, Chitosan, Methocel, Carbapol, Polyacrylates, polyvinyl acetate and polycarbonate.

2. Ion tropic Gelation Method: This method is based on the ability of polyelectrolytes to link with counter ions and to form beads. Because of the truth that the usage of alginates, CMC and Chitosan for the encapsulation of drug and even cells, ion tropic gelation method has been broadly used for this cause the herbal polyelectrolytes in spite, having belongings of coating at the drug centre and acts as drug retardants, contains high-quality anions on their chemical form. Those anions paperwork meshwork structure by way of combining with the polyvalent cations and prompt gelation by using binding especially to the anion blocks.

The hydrogel beads are produced by means of way of dropping a drug-loaded polymeric answer into the aqueous answer of polyvalent cations.

3. Emulsion Solvent Diffusion Method: This technique is more useful than other techniques. The medicament is dissolved within the natural solvent. Polymers are dispersed in an aqueous solvent despite the fact organic solvent is melting.

Out of the emulsion droplets, the natural solvent diffuses steadily into the surrounding aqueous phase and into the droplets; the aqueous section diffuse through which the drug crystallizes.

4. Single Emulsion Technique: Micro particulate corporations of natural polymers occur in this method, *i.e.,* By manner of single emulsion technique, the ones of proteins and carbohydrates are prepared.

In an aqueous medium, the natural polymers are dispersed or dissolved and exposed through dispersion in a non-aqueous medium like oil with the assist of change in linking agent.

5. Double Emulsion Technique: The formation of more than one emulsions or the double emulsion entailed in this approach which consisting of multiple emulsion *i.e.,* w/o/w. This method may be used with natural as well as synthetic polymers

6. Polymerization Technique:

a) Normal Polymerization: With the use of tremendous strategies as suspension, emulsion, precipitation, bulk, and micelles polymerization, regular polymerization is performed. With the resource of bulk polymerization, herbal polymers are formed.

b) Interfacial Polymerization: On the interface, it consists of the reaction of numerous monomers to form a film of polymer contains most of the two immiscible liquid phases that basically envelop the dispersed.

7. Phase Separation Coacervation Technique: It's far based completely on the precept in organic

segment, lowering the solubility of the polymer to have an influence on the development of polymer-rich phase known as coacervates.

In answer to the polymer, the drug remains dispersed, and to the system, and the incompatible polymer is added, which makes the first polymer to phase separate and immerse the drug debris [9].

Characterization of Prepared Microspheres:

1. Micromeritic Properties: The prepared microspheres can be distinguished by their micrometric properties like microsphere particle size, Bulk density, Tapped density, Carr's compressibility index, Hausner's ratio, and angle of repose [10].

a) Bulk and Tapped Density: Bulk and tapped densities were measured by using 50 ml of the graduated cylinder. A carefully weighed amount of sample passed through a glass funnel.

The sample poured in the cylinder was tapped mechanically 100 times. Then tapped volume was noted down, and bulk density and tapped density were calculated by using the following formula. It was expressed in g/cm^3.

Bulk density (ρb) = Mass of microspheres (M)/Volume of microspheres after tapping (Vb)

Tapped density (ρt) = Mass of microspheres (M)/Volume of microspheres after tapping (Vt)

b) Carr's Compressibility Index or Compressibility index (C.I.) or Carr's index value of microspheres was calculated according to the following equation

% Compressibility index = (Tapped Density-Bulk Density/Tapped Density) ×100

c) Hausner's Ratio: Hausner's ratio of microspheres was identified by comparing the tapped density to the bulk density using the equation.

Hausner's ratio = (Tapped density/Bulk density) × 100

d) Angle of Repose: The maximum angle which is formed between the surface of a pile of powder and the horizontal surface is called the angle of repose.

$$\tan \theta = h/r$$

Where T = angle of repose, h = height of the circle formed by the powder heap, r = radius of the heap

2. Particle Size Distribution of Microsphere: [11]

Particle Size Analysis: Particle size analysis of drug-loaded Eudragit microspheres was performed by optical microscopy using a compound microscope. The slide containing Eudragit microspheres was mounted on the stage of the microscope, and diameter of at least 300 particles was measured using a calibrated ocular micrometer. The average particle size of microspheres was determined by the total size of the microspheres divided by the number of microspheres

3. Morphological Study using Scanning Electron Microscopy (SEM): SEM technique is used for determining the surface morphology of the microspheres. The SEM sample is prepared by sprinkling the powder on the tape stuck attached to an aluminium stub.

The stubs are coated using the mixture of gold and palladium at a thickness of 250–450Å under an argon atmosphere in a high vacuum evaporator at a voltage of 20 KV, current 10 mA, and low pressure. Photomicrographs are taken on the random screening of coated samples using SEM [12].

4. Determination of % Yield of Microspheres: Thoroughly dried microspheres were collected and weighed accurately. The percentage yield was then calculated using formulae given below [13].

Percentage yield = Weight of obtained microspheres/Total weight of drug and polymer ×100

5. Buoyancy Studies: *In-vitro* floating tests can be performed in USP type II dissolution test apparatus by spreading the floating microspheres on a simulated gastric fluid (pH 1.2) containing the surfactant. The media is stirred at 100 rpm at 37± 0.5°C. After specific intervals of time, both the fractions of microspheres (floating and settled microspheres) are collected and buoyancy of the floating microspheres is determined by using formula [14]

Buoyancy (%) = Qf / Qf + Qs × 100

Where, Qf and Qs are the masses of floating and settled hollow microspheres, respectively

6. Drug Entrapment Efficiency: Formulated microsphere equivalent to 100 mg of the drug were taken for evaluation. The amount of drug entrapped

was estimated by crushing the microsphere and extracting with aliquots of 0.1N HCl repeatedly.

The extract was transferred to 100 ml volumetric flask, and the volume was made up using 0.1 N HCl. The solution was filtered, and the absorbance was measured at Specific nm against blank. The amount of drug entrapped in the microsphere was calculated by following formula [15]

% Entrapment Efficiency = Amount of drug actually present / Theoretical drug load expected × 100

Drug Content: The drug content of Microspheres was identified by dispersing 50 mg formulation in 10 mL acetone, followed by mixing with a magnetic stirrer for 12 h to wet the polymer and to extract the drug. After filtration through a Whatman filter, the drug concentration in the ethanol phase was determined spectro-photometrically at their relevant nm by making the desired dilution with 0.1N HCl. Each determination was made in triplicate. The percentage drug entrapment and yield are to be calculated as follows [16]:

% Drug loading = (Actual drug content/Weight of microspheres) × 100

Scientific Approaches: An exhaustive literature was made here for formulating floating micro-spheres using numerous scientific approaches by different authors. This article highlights diverse scientific approaches adapted for preparing Floating microspheres of a diverse groups of the drug for past years. Earlier attempts so far did on Floating microspheres were shown below.

Shivani S *et al.,* (2018) Formulated floating microsphere of Esomeprazole magnesium trihydrate by double emulsion solvent diffusion technique using polymers like ethyl cellulose in different ratios, HPMC different grades (K4M, K15M). The entrapment efficiency, percentage yield, and particle size enhanced with the blend of ethyl cellulose and HPMCK15M than Ethylcellulose and HPMCK4M. Based on the entrapment efficiency, the entrapment efficiency, percentage of the yield as well as particle size improved with a combination of Ethyl Cellulose & HPMCK15M than Ethyl Cellulose & HPMC k4M [17]. Rukhsar Khan *et al.,* (2018) Developed Floating microspheres of Levofloxacin by a solvent evaporation method using polymers like Eudragit and Ethylcellulose in different combinations. Prepared microspheres were evaluated for particle size, % buoyancy, *in-vitro* release study, and stability studies. The percentage buoyancy was found to be in the range of 67.12% to 94.21%. The good buoyancy behavior of the microspheres revealed that the microspheres are hollow in nature and retained for more than 12 h in the upper part of the GIT in order to enhance gastric residence time [18].

Swathi Chilukala *et al.,* (2016) developed floating microspheres of cefditoren Pivoxel by solvent evaporation technique using hydroxyl propyl methylcellulose (HPMC) K4M and ethyl cellulose as the rate-controlling polymers. The optimization of the formulation was done by 3^2 factorial designs using two factors; a total amount of polymer (X1) and concentration of ethyl cellulose (X2) as independent variables. The formulated floating microspheres were characterized by evaluating their yield, particle size, encapsulation efficiency, *In-vitro* drug release, buoyancy, surface morphology. The optimized formulation had shown 91.5 ± 1.35% of drug release after 12 h and 75 ± 0.92% of entrapment efficiency. All the formulations had good buoyancy, which was floated over 12 h in the dissolution medium [19].

Vani Prasanna Tubat *et al.,* (2016) Developed floating pulsatile microspheres of Ivabradine Hydrochloride by nonaqueous solvent evaporation method, and statistical optimization was done using software-based response surface methodology in which three process variables were of utmost importance such as stirring speed, stirring time, and polymer concentration. The desired responses were % entrapment efficiency, % of buoyancy, and % DE at 20 min of microspheres. Optimization was done by fitting experimental data to the software program (Minitab). Obtained microspheres were subjected to different evaluation parameters, which are essential in the development of the dosage form. The optimized batch of formulation showed satisfactory drug entrapment efficiency of 88.56 ± 1.12, % of buoyancy of 91.42 ± 1.09, and %DE at 20 min of 64.4 ± 0.36.

Scanning electron microscopy analysis revealed that particles were spherical with a smooth surface.

Particles were free-flowing, and its average particle size 794 ± 1.43 μm. The developed, optimized batch of microspheres maintained lag phase during floating in acidic medium (simulated gastric fluid) for 5 h followed by the pulsatile release of Ivabradine HCl within 30 min in phosphate buffer PH 7.4 (Simulated intestinal fluid). FTIR and DSC studies revealed that there was no interaction between Ivabradine HCl and Eudragit S100. So in this present work, Ivabradine HCl floating pulsatile microspheres were successfully formulated made using response surface methodology [20].

Tubati VP *et al.,* (2017) Formulated gastroretentive Floating microspheres of an antiulcer drug misoprostol by an emulsification solvent evaporation technique using hydroxypropyl methyl- cellulose (HPMC K 100M) and ethyl cellulose. The percentage yield and drug entrapment efficiencies of these floating micro-spheres were within the range between 70 ±2.8 to 98 ± 2.9 % and 39.27 to 82.39 %, respectively. The determined mean particle size for all the microspheres was 250 ± 7.28 to 400 ± 2.32 μm. The flowability of these microspheres was found good. An HPLC method with ultra-violet (UV) detection was selected for the method of analysis. The drug release was found to delay for 12 hours with the increasing drug to polymer ratio. The drug release kinetics followed Korsmeyer-Peppas and Higuchi model with an anomalous (non-Fickian) diffusion mechanism for the drug release. The FTIR and DSC studies showed that there was an absence of chemical interaction between the drug and the excipients. The *in-vitro* drug release from misoprostol floating microspheres showed the drug release was dependent on the drug to polymer ratio. The drug release was found delayed with the increasing drug to polymer ratio [21].

Swetha Kallepu *et al.,* (2016) Nimodipine encapsulated floating microspheres were formulated and characterized for enhancing residence time of drug in GIT using ethyl cellulose and Eudragit S100 as polymers by a solvent evaporation method. Microspheres were characterized for their micrometric properties, floating behavior, entrapment efficiency, scanning electron microscopy (SEM), X-ray diffraction, differential scanning Colorimetry, and *in-vitro* drug release. Floating microspheres were successfully prepared by a solvent evaporation method. SEM images showed that microspheres prepared with different concentrations of polymer and emulsifier were spherically shaped with a smooth surface. The prepared microspheres also showed good flow properties. Size of microspheres was in the range of (90 ± 1.02)-(145 ± 1.34) μm. Microspheres were capable of floating for 12 h. As the polymer concentration increases, *in-vitro* drug release was decreased. However, the release was controlled by polymer concentration for a longer period. Conclusion: The optimized formulation showed good results for all the evaluation parameters. Hence, it can be concluded that the developed formulation is a potential dosage form for nimodipine [22].

Ammar HO *et al.,* (2016) Developed Risperidone Floating microparticles were prepared using Eudragit S100, hydroxypropylmethylcellulose (HPMC), Gelucires (Gelucire 43/01 pellets, Gelucire 44/14 and Gelucire 50/13), Geleol mono and diglyceride NF, glyceryl monostearate, Compritol 888 ATO, methyl-beta cyclodextrin (MbCD) and hydroxypropyl-beta-cyclodextrin (HPbCD), by emulsion solvent diffusion technique. *In-vitro* experiments were conducted to optimize formulation parameters regarding floating ability, yield value, drug loading, and *in-vitro* release properties.

The best formula was investigated for its *in-vivo* floating ability and for its pharmaco-kinetics as well as its extrapyramidal side effects in human volunteers. The optimized floating micro-particles showed promising *in-vitro* experiment performance with floating ability up to 95.93% for 12 h. Also, this floating ability was confirmed using *in-vivo* x-ray studies. Pharmacokinetics studies revealed significant ($p < 0.05$) lower C_{max}, longer $T_{max,}$ and higher AUC values for the optimized formula compared to the marketed oral product (Risperidal® 4 mg tablets), indicating gradually release properties which lead to high treatment efficacy of the drug with obvious reduced extrapyramidal side effects.

These results proved that formulating risperidone as floating micro-particles is a suitable dosage form for overcoming risperidone side effects [23].

Rukhsar Khan *et al.,* (2018) Developed a site-specific drug delivery system for the controlled release of Levofloxacin by solvent evaporation method for eradication of H. pylori for the treatment of peptic ulcer. The drug was encapsulated with Eudragit and Ethylcellulose in various combinations of polymers ratios. The prepared microspheres are subjected to evaluation for particle size, % buoyancy, *in-vitro* release study, and stability studies. The percentage buoyancy was found to be in the range of 67.12% to 94.21%. The good buoyancy behaviour of the microspheres revealed that the microspheres are hollow in nature and retained for more than 12 h in the upper part of the GIT in order to enhance gastric residence time. The prepared formulations can be tested clinically to assure *in-vivo* performance. The current study compared the combination of polymers and revealed their effect on drug release and various other parameters for the preparation of floating microspheres [24].

S. Indira *et al.,* (2015) Developed multiple unit type oral floating microspheres of Balofloxacin prepared by solvent diffusion method using polymers Ethylcellulose, HPMCK4M, and Eudragit RSPO in different ratios to prolong gastric residence time. The prepared Microspheres were evaluated for particle size, percent yield, entrapment efficiency, flow properties, SEM, buoyancy test, *in-vitro* drug release studies, everted sac test for bio adhesion and *in-vitro* absorption by everted sac technique. The prepared microspheres were found to be discrete, spherical in shape, free-flowing and remain buoyant for more than 12 h. *In-vitro* drug release was found to be 80-98% at the end of 12 h. *In-vitro* absorption studies indicate a significant absorption of the drug in the stomach. The everted sac test revealed that microspheres also exhibit bio adhesion property. From our studies, it is evident that these floating microspheres can be explored for the development of gastro retentive drug delivery system of Balofloxacin [25].

Ramalingam Nethaji *et al.,* (2015) formulated floating microspheres of Ofloxacin for prolongation of gastric residence time with an aim to improve bioavailability. Eight formulations were prepared by different concentrations of ethylcellulose, HPMC K4M, and HPMCK15M by non-aqueous solvent evaporation technique. Depending upon the drug-polymer ratios, the percentage yield is found between 86.75±0.96% to 95.93±0.94%, and entrapment efficiency was 70.47± 0.96% to 91.28± 0.82% in all formulations. Microspheres showed a good specificity, spherical and uniform in shape with smooth surface and the mean particle size significantly increase with increasing polymer concentration and it was in the range between 182.41±0.54 to 229.43±0.48 µm. The percentage *in-vitro* buoyancy of the floating microspheres was in the range of 70.37 ± 0.68% to 86.07± 0.86%. *In-vitro* drug release studies were performed in simulated gastric fluid; it is revealed that formulation codes OF-III and OF-VII were found in 97.81±0.94% and 98.80±0.68% drug releases at the end of studies when compared to all batches due to increases in polymer concentration. Stability studies of selected floating microspheres showed good results [26].

D. Kusuma *et al.,* (2017) formulated floating microspheres of Acebutolol is solvent diffusion evaporation technique. Preformulation studies have done to formulate the floating microspheres, Acebutolol as API, and three polymers were used, namely Cellulose Acetate (F1), EdurgitS100 (F2), Acrycoat S100 (F3). For the above formulations, all the evaluation parameters (SEM studies, buoyancy studies, the *in-vitro* studies, Floating time) were conducted. The microspheres were placed in a 6.8 pH phosphate buffer containing surfactant tween 80 to stimulate gastric condition. The drug release from floating microspheres found to be 84.22 ±0.29, 75.19 ±1.99, 67.59 ±1.97for F1, F2, and F3 respectively [27].

Peeyush Bhardwaj *et al.,* (2017) Developed floating microspheres of Metronidazole as a model drug, using the modified solvent diffusion evaporation technique. Eudragit S100 and Eudragis RS100 were used in different ratios as polymers for the development of microspheres. The micro-spheres were characterized for surface morphology by SEM, yield, buoyancy, incorporation efficiency, and micrometric properties. The *in-vitro* drug release studies were performed in simulated gastric fluid at pH 1.2. Different kinetic models were also applied on drug release from selected formulations. Stability studies were additionally subjected for optimized formulations. The yield of microspheres was found to be good. Microspheres showed

satisfactory flow properties. SEM confirmed the spherical size, perforated smooth surface, and hollow cavity in them. Microspheres exhibited floating properties for more than 10 h. Stability studies showed no significant change in residual drug content of floating Microspheres [28].

Vivekananda. K *et al.,* (2018) Developed Floating hollow microparticles (Microballons) of Nifedipine using Eudragit S100 as polymer by solvent evaporation method so as to prolong the gastric residence time as well as the drug release. The effect of variables like a drug to polymer ratio and volume of solvents on the physical characteristics of microparticles was investigated. The particle size distribution of the microparticles was determined using optical microscopy. The % drug loading and % entrapment efficiency of the microparticles were estimated by UV spectro-photometry. The surface morphology of microparticles was evaluated using scanning electron microscopy. *In-vitro* buoyancy studies were performed in USP Type II (rotating paddle) dissolution apparatus. *In-vitro* dissolution studies were performed in USP Type I dissolution apparatus with 0.1 N HCl (pH 1.2). Among all the prepared Microparticles, F2 was found to demonstrate an average particle size of 227µ, prolonged buoyancy, and complete drug release in 8 hours. Therefore, it can be concluded that F2 would be the most suitable formulation [29].

Ali Khidher Abbas *et al.,* (2018) Developed Enalapril Maleate loaded floating microspheres by ionotropic gelation technique using a hydrophilic carrier. Eleven developed formulations of floating microspheres were prepared by using different concentrations of sodium alginate, iota-carrageenan, sodium bicarbonate, calcium chloride, and the drug. These microspheres were characterized using a diversity of parameters like micrometric properties, percentage yield, entrapment efficiency, *in-vitro* buoyancy, *in-vitro* drug release, and kinetics of drug release. The optimum formula was evaluated and identified for drug-excipients compatibility using Fourier transform-infrared spectroscopy (FT-IR), surface morphology, powder X-ray diffraction (XRD), and differential scanning Calorimetry (DSC). Among eleven formulations, F4 was selected as the optimum formula since it provides a faster and premium release of drug from the matrix (91.4%). Kinetics of drug release was found to depend on both diffusion and erosion mechanisms, as the correlation coefficient (R2) was best fitted with Korsmeyer's model, and the release exponent (n) was shown to be between 0.43 and 0.84. Scanning electron microscopy images demonstrated spherical, discrete, and freely flowing microspheres with a particle size of 199.4±0.04 µm. Optimum buoyancy properties, percentage yield, and drug entrapment efficiency were achieved. FT-IR showed no interaction between Enalapril and the polymers. DSC and XRD showed the miscibility of the drug with the polymers while maintaining the stable crystalline properties of Enalapril loaded in the prepared microspheres. So the developed floating microspheres of Enalapril Maleate can be considered a promising controlled drug delivery system, thereby improving patient compliance [30].

Amul Mishra *et al.,* (2018 Developed a floating Microsphere of Metformin hydrochloride by emulsion solvent evaporation technique using Eudragit S100, Ethylcellulose, Cellulose acetate, HPMC as polymer. The prepared microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm). Microspheres are characteristically free-flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 µm. At the end of 12 h. The cumulative percentage release of Metformin Hydrochloride from Ethylcellulose microspheres was found to be 72.48%, 83.51%, 79.85%for formulations A1, A2, A3, respectively. The percentage cumulative drug release from cellulose acetate microspheres was found to be 95.52%, 90.13%, 86.31% for formulations A4, A5, A6, respectively. The percentage cumulative drug release for Eudragit S100 and HPMC microspheres were found to be 85.29%, 80.0%, 76.05% for formulations A7, A8, A9, respectively [31].

Suggala Ajay *et al.,* (2018) Floating microspheres of Tolcapone were prepared by ionotropic gelation method with the aim of increasing the gastric residence time and for controlled release using different polymers like HPMC K4M and HPMC K15M as rate retarding agent. The FTIR studies indicated no significant interaction observed between drug and excipients. Among all the

prepared formulations, the F12 formulation showed excellent flow properties. Percent yield, % entrapment efficiency. The swelling index of optimized formulation was found to be 98.45%, 98.02%, and 98.50%, respectively. The % buoyancy was excellent, with approximately 98.42% of the micro-spheres floating upto 24 h. The Cumulative % drug released from F12 microspheres was found to be 98.26±5.05% within 12h and compared with the marketed product 91.25±5.00%. The optimized formulation F12 best fitted into zero-order and Higuchi kinetics indicating diffusion controlled drug release pattern. SEM studies showed the spherical shape and revealed the presence of pores on the surface of the floating microspheres, which was responsible for floating ability. From stability studies, optimized microspheres were stable for 6 months. The F12 formulation showed better results with HPMC K15M compared with HPMC K4M as rate retarding polymer. These results indicated that the Tolcapone-loaded microspheres could potentially be exploited as a delivery system with controlled drug release in the effective management of Parkinson's disease [32].

Dhurke Rajeshri *et al.,* (2019) Developed floating microspheres of Metoprolol tartrate by a solvent evaporation method using ethyl cellulose as a polymer for gastroretentive delivery containing using factorial design and also to investigate the effect of different process variables on the formation of the microsphere. The effect of the independent process variables like polymer concentration, surfactant concentration, stirring speed, continuous phase, and disperse phase on drug entrapment and particle size was optimized using 2^3 factorial designs. Response surface graphs were plotted using Box-Behnken design. The optimized formulation of floating micro-spheres was characterized for various physic-chemical properties, surface morphology, and drug excipients interaction. The optimized formulation F4 showed drug entrapment efficiency of 77%, having a particle size of 56±1.6 μm. The drug was released by Fickian diffusion mechanism with cumulative drug release of 98% for 12 h as compared to other formulations. Microspheres floated well over 12 h in simulated gastric fluid (pH 1.2). There was no incompatibility between drug and excipients, and the surface of the microsphere was smooth with porous structure. Probability factor, R2 values, and lack of fit values were significant, showings that the model was significant. The observed responses coincided well with the predicted values given by the optimization technique. The combined effect of different process variables and its main effect on response can be studied well by using factorial design, and an optimized formulation with desired properties can be obtained with minimum experiments [33].

Manjunath K *et al.,* (2019) Developed floating microspheres containing Candesartan cilexetil by using the solvent evaporation method. The micro-spheres were formulated using different polymers like ethyl cellulose, HPMC K4M, and Eudragit RSPO100 in different concentrations and combinations. The prepared floating microspheres were characterized for their percentage yield (95.44-98.52%), drug entrapment efficiencies (71.52-97.87 %), and percentage buoyancy (93.45-98.66%). The FTIR and DSC studies revealed the absence of interactions between the drug and selected polymers. *In-vitro* release studies were performed in 0.1 N HCl, which showed a drug release of 97.62 % at 24 h in case of formulation (F7). Fitting the *in-vitro* drug release data to Korsmeyer's equation indicated that Fickian diffusion is the mechanism of drug release [34].

Ramya Sri Sura *et al.,* (2019) Formulated floating and mucoadhesion microspheres of Etodolac using ionic gelation method. The floating and mucoadhesion microspheres were studied for micro-merits properties were found to be within limits. The percentage yield of floating microsphere formulation F1 to F6 and mucoadhesive micro-spheres M1 to M3 were in the range of 77.14 ± 0.64 to 92.74 ± 0.74%. The *in-vitro* buoyancy of formulation F1 to F6, it was range from 71.96 ± 1.04 to 82.96 ± 1.07. Among all the formulations, F6 was found to be the highest *in-vitro* buoyancy, 82.96 ± 1.07. The results also showed that the larger the particle size, the longer the floating time. The entrapment efficiency of floating microspheres F1 to F6 and mucoadhesive microspheres were in the range of 77.43 ± 2.72 to 98.11 ± 2.59. Formulations prepared with sodium alginate alone have shown maximum drug release at 12 h in the ratio of 1:3. Formulations prepared with sodium alginate along with HPMC K 4M

retard the drug release. Among all formulations of floating microspheres, F3 was considered as optimized for floating microspheres. From the release kinetics data, it was evident that floating optimized formulation follows zero-order release kinetics. From the dissolution data of mucoadhesive microspheres by ionic gelation method M1, the formulation has shown maximum drug release at 12 h. When an increase in the polymer concentration retards, the drug release more than 12 h. Hence, M1 was considered as an optimized formulation for mucoadhesive microspheres, and it was followed zero-order release kinetics [35].

Someshwar Tiwari *et al.,* (2019) Formulated Famotidine Floating microspheres. These micro-spheres are free-flowing powders, gastric contents for a prolonged time. Hence faster dissolution of dosage form results in faster absorption and onset of action. Floating micro-spheres are absorbed from the mouth, pharynx, and esophagus as the saliva passes down the stomach. In such cases, the bioavailability is greater than those observed for the conventional dosage form. Different polymers such as ethylcellulose, sodium alginate were optimized with different concentrations and varying the ratios in order to get the sustained release profile over a period of 24 h. All the formulations were evaluated for *in-vitro* buoyancy, entrapment efficiency, and *in-vitro* drug release profile. The results revealed that the present buoyancy is more than 70% after 24 hrs. The mean particle size of microspheres was in the range of 102.33-420.53 µm. *In-vitro* release of floating microspheres of Famotidine HCL was found to be in the following order, H1>HE1>H2> HE4>E1>HE2>H3>HE3>HE5>E2>E3. H1 was found to be the best formulation among all other formulation prepared as it releases Famotidine HCL 98.84 % in a sustained manner with constant fashion over an extended period of time (after 24 h) [36].

Sanjay Kumar Mishra *et al.,* (2019) Developed Floating microspheres of Nizatidine were prepared by solvent evaporation (oil-in-water emulsion) technique. In this, 225 mg poly(methyl methacrylate) (PMMA) were dissolved in a mixture of dimethylformamide and dichloromethane (1:1) at room temperature. And 75 mg Nizatidine hydrochloride was added to the above mixture. This was poured into 250 ml water containing 0.02% Tween 80, maintained at a temperature 30-40 ºC and subsequently stirred at ranging agitation speed for 20 min to allow the volatile solvent to evaporate. The microspheres formed were filtered, washed with water, and dried in a vacuum. The prepared floating microspheres were characterized in a different way, like size distribution 131.4 ± 1.6 µm and 89.5 ± 1.4% entrapment efficiency was found, a floating *in-vitro* test of optimized floating microspheres formulation was studied in SGF (pH 1.2). The percent cumulative amount of drug release was found 87.2 ± 2.6% in SGF (pH 1.2), 90.2 ± 3.5% in SIF (pH 6.8) and 93.2 ± 3.5% in PBS (pH 7.4) up to 24 h. The ulcer protection of the microspheres formulation was 79.84% as compared to the Nizatidine pure drug (66.05%) in ulcer-induced rats. The C-max value of Nizatidine as obtained from the graph was 575.14 ± 55.43 mg/ml with T_{max} value 2 h and for the formulation was 206.58 ± 7.71 mg/ml. So the developed Floating microspheres provide the possibility of enhancing the bioavailability and control the release of formulation exhibiting absorption window by prolonging the gastric emptying time of the dosage form, ensuring availability of the drug at the absorption site for the desired period [37].

Mahmoud M. Ahmed *et al.,* (2019 prepared floating hollow microspheres encapsulating Sorafenib (SFN) using an emulsion solvent evaporation technique with ether and ethanol as solvents. Ethylcellulose and carbopol 934P were used as the encapsulating carriers to enhance its oral bioavailability The effects of formulation parameters like solvent volume ratio and drug to polymer ratio (D: P ratio), encapsulation efficiency percentage EE%, floating percentage, and release of SFN after 12 h (Rel12) were investigated and analyzed using a (32) full factorial design. The floating percentage of the microspheres was found to be 76.5%. The *in-vitro* drug release from these hollow microspheres followed the Higuchi model equation. The *in-vivo* results showed that approximately 1.96-fold improvement in the relative bioavailability of the microspheres compared with that of the commercial tablet. The results demonstrate that the hollow microspheres with good gastro-floating ability are a promising delivery system to enhance SFN bioavailability [38].

Sanjay K. Mishra *et al.,* (2019) Developed Nizatidine hydrochloride Floating microspheres by Solvent evaporation (oil-in-water emulsion) technique. It was observed that on increasing the concentration of the drug, the entrapment efficiency increased. While further increasing drug concentration, the entrapment efficiency gradually decreased. The average particle size of floating micro-spheres reduces with an increased in temperature. Narrow size distribution 131.4+1.6 µm and 89.5+1.4% entrapment efficiency was found to a formulation at 37 ºC temperature.

The results showed that the percentage buoyancy of floating microspheres formulation was significantly decreased after 5 h. The percent cumulative amount of drug release was found 87.2+2.6% in SGF (pH 1.2), 90.2+3.5% in SIF (pH 6.8) and 93.2+3.5 % in PBS (pH 7.4) up to 24 hrs. The results clearly suggest that floating microspheres formulation could also be utilized for sustained and drug delivery purposes [39].

Chhitij Thapa *et al.,* 2020) Prepared an Enalapril Maleate (EnM)-loaded floating microsphere by solvent evaporation method with minimum particle size, maximum drug loading, and drug entrapment efficiency. Formulations were prepared by varying drug-to-polymer ratio (A), solvent ratio (B), and stirring time (C). "Box–Behnken's design" (3 factors × 3 levels) was utilized for optimization. The independent variables were polymer to- drug ratio (A), solvent ratio (B), and stirring time (C), while particle size (R1), drug loading (R2), and entrapment efficiency (R3) were considered as dependent variables.

EnM-loaded alcohol microsphere (Formulation-A) was prepared and optimized. Both Formulation-A and EnM-loaded acetonitrile microspheres (Formulation-B) were subjected to morphological, micrometric, characterization, and *in-vitro* release studies. The particle size, drug loading, and entrapment efficiency of Formulation-A and Formulation-B were 143 ± 27.75 µm, 37.31% ± 5.73%, and 76.89% ± 4.97%, and 158.13 ± 25.1 µm, 40.13% ± 6.12%, and 99.19% ± 1.14%, respectively. The cumulative drug releases of Formulation-A and Formulation-B were 90.52% ± 4.11% and 86.23% ± 3.81%, respectively. Both formulations followed the Higuchi model of drug release. EnM-floating microsphere was effectively prepared, and both formulations showed excellent continuous release properties for more than 12 hours [40].

Suggala Ajay *et al.,* (2018) Developed gastro retentive floating microspheres of Entacapone by ionotropic gelation method with the aim of increasing the gastric residence time and for controlled release. The polymeric mixture of Sodium alginate and HPMC K4 was used as polymers. Sodium bicarbonate was used as the gas-forming gent. Prepared Microspheres were characterized for the Micromeritic properties, incorporation efficiency, buoyancy test, SEM analysis, FTIR, and *in-vitro* diffusion studies.

The diffusion studies were carried out in 0.1N HCl, and the results were applied to various kinetic models. Among the total 14 formulations, F14 was optimized. The % yield of F14 formulation was found to be 98.03%. Based on optical microscopy, the particle size was 65.23 ± 0.05 µm. The % buoyancy, % entrapment efficiency, and swelling index of F14 formulation were 98.16%, 97.54%, and 97.67%, respectively.

CONCLUSION: The cumulative % drug release of F14 formulation was 97.99 ± 5.05% in 12 h when compared with marketed product 95.12 ± 5.01 in 1 h. SEM studies showed the particles were in a spherical shape. Hence the formulated and prepared floating Entacapone microspheres may establish to be a potential candidate for safe and effective sustained drug delivery and improve the bioavailability in the management of Parkinson's disease [41].

ACKNOWLEDGEMENT: Nil

CONFLICTS OF INTEREST: Nil

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How to cite this article:
Pavan AR, Grace XF and Ramakrishnan SR: Floating microspheres: a novel emerging trend in gastro retentive drug delivery. Int J Pharm Sci & Res 2021; 12(6): 3019-33. doi: 10.13040/IJPSR.0975-8232.12(6).3019-33.

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