IJMPR 2024, 8(1), 87-93

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 5.273

AN UPDATED REVIEW ON FLOATING MICROSPHERES - A MODIFIED DOSAGE FORM

Harpreet Kaur Sandhu*, Kapil Kumar and Vaishali Rajput

Division of Pharmaceutics, Global Institute of Pharmaceutical Education and Research, Kashipur, Uttarakhand, India.

Article Received on: 21/11/2023
Article Revised on: 11/12/2023
Article Accepted on: 01/01/2024

***Corresponding Author**
Harpreet Kaur Sandhu
Division of Pharmaceutics, Global Institute of Pharmaceutical Education and Research, Kashipur, Uttarakhand, India.

ABSTRACT
Floating microspheres is a novel drug delivery system used exclusively for gastro-retentive preparationsbased on a non – effervescent approach. Gastro-retentive floating microspheres are low-density systemsthat have sufficient buoyancy to float over gastric contents and remain in stomach for prolongedperiod. The drug is released slowly at desired rate resulting in increased gastric retention withreduced fluctuations in plasma drug concentration. suitable for the continuous or late release of oral formulations, thus controlled drug delivery system. Floating microspheres are, in a strict sense, spherical empty particles without a core. Floating microspheres are especially gaining attention due to their wide applicability in the targeting of drugs to the stomach. Floating microspheres improve patient compliance by decreasing dosing frequency, better therapeutic effect of short half-life drugs can be achieved**.** Enhanced absorption of drugs which solubilize only in stomach. Floating microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core. Present review articles deals with different aspect of floating microspheres.

KEYWORDS: Floating microspheres, buoyancy, gastro-retentive.

INTRODUCTION

The primary aim of oral controlled drug delivery ,the most preferable route of drug delivery system is to achieve better bioavailability and release of drug from the system which should be predictable and reproducible, easy for administration, patient compliances and flexibility in formulation for effective therapy or to improve therapeutic efficiency of the drug through improved bioavailability.[1] Gastric retention can be achieved by the mechanism of mucoadhesive or bioadhesion systems, expansion system, high density systems, magnetic systems, super porous hydrogels, raft forming systems, low density system and floating ion exchange resins.[2]

Microspheres are the hollow spherical particles made up of polymeric substances in which drug is entrapped or dispersed throughout the polymeric matrix. Its size ranges from 1 to 1000 µm. Biodegradable polymers are frequently used for the development of microsphere matrixes such as polylactic acid and copolymer of lactic acid and glycolic acid. Apart from them, there is an extensive range of microspheres prepared from albumin, albumin dextran sulfate, and fibrinogen.[3] Microparticulate systems is advantageous because microspheres can be ingested or injected; they can be tailored for desired release profiles and used for site-specific delivery of drugs and in some cases can even provide organ-targeted release. Microspheresare small in size and therefore have largesurface to volume ratios.[4]

The use of floating microspheres in pharmaceuticals have a number of advantages[5,6,7]

- Improve drug absorption because of increase gastric residence time and more time spent.
- by the dosage form at its absorption site thereby increasing bioavailability of encapsulated drug.
- Controlled or sustained drug delivery system.
- Delivery of drugs for local action in the stomach.
- Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlledrate.
- Treatment of gastrointestinal disorders such as gastro oesophageal reflux.
- Simple and convential equipment for manufacture.
- Ease of administration and better patient compliance.
- Less frequent dosing.
- Possibly reduced side effects of drugs for prolonged administration.
- Avoiding peak and valley curves in plasma drug concentration.
- Site - specific drug delivery.
- Superior to single unit floating dosage forms as such microsphere's releases drug
- uniformly and there is no risk of dose dumping.
- Avoidance of gastric irritation, because of sustained release effect.
- Better therapeutic effect of short half-life drugs can be achieved.
- Improved receptor activation selectivity.

- Extended time over critical (effective) concentration.
- Less inter- and intra-subject variability.
- Flexibility in dosage form design.

Disadvantages of Floating Microspheres[8,9]

- Floating systems are not feasible for those drugs that have solubility or stability problems.
  in gastric fluids.
- Drugs such as Nifedipine, which is well absorbed along the entire GI tract and whichundergo significant first – pass metabolism, may not be desirable.
- Gastric retention is influenced by many factors such as gastric motility, pH and presenceof food.
- Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulatedas drug delivery systems.

APPROACHES TO GASTRIC RETENTION

1. Floating Systems

Floating systems are low-density systems thathave sufficient buoyancy to float over thegastric contents and remain in the stomach fora prolonged period. While the system floatsover the gastric contents, the drug is releasedslowly at the desired rate, which results inincreased gastro-retention time and reducesfluctuation in plasma drug concentration.[10]

2 Bio/Muco-adhesive Systems

Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules and increase the residence time of the dosage form at the site of absorption. The drugs which have local action or those which have maximum absorption in gastrointestinal tract (GIT) require increased duration of stay in GIT. Thus, mucoadhesive dosage forms are advantageous in increasing the drug plasma concentrations and also therapeutic activity.[11]

Binding of polymersto mucin/epithelial surface can be divided intothree broad categories.

- Hydration-mediated adhesion.
- Bonding-mediated adhesion.
- Receptor-mediated adhesion.

3. Swelling and Expanding Systems

These are dosage forms, which afterswallowing, swell to an extent that preventstheir exit from the pylorus. As a result, thedosage form is retained in stomach for a longperiod of time. These systems may be namedas “plug type system”, since they exhibittendency to remain logged at the pyloricsphincter.[12]

4. High density systems

These systems with a density of about 3 g/cm3are retained in the rugae of stomach and arecapable of withstanding its peristalticmovements. A density of 2.6-2.8 g/cm3 actsas a threshold value after which such systemscan be retained in the lower parts of thestomach. High-density formulations includecoated pellets. Coating is done by heavy inertmaterial such as barium sulphate, zinc oxide,titanium dioxide, iron powder.[13]

5. Incorporation of passage delaying food agents

Food excipients like fatty acids e.g. salts ofmyristic acid change and modify the pattern ofstomach to a fed state, thereby decreasinggastric emptying rate and permittingconsiderable prolongation of release. Thedelay in gastric emptying after meals rich infats is largely caused by saturated fatty acidswith chain length of C10-C14.[14]

6. Ion exchange resins

Ion exchange resins are loaded withbicarbonate and a negatively charged drug isbound to the resin. The resultant beads arethen encapsulated in a semi-permeablemembrane to overcome the rapid loss ofcarbon dioxide. Upon arrival in the acidicenvironment of the stomach, an exchange ofchloride and bicarbonate ions take place. As aresult of this reaction carbon dioxide isreleased and trapped in the membranethereby carrying beads towards the top ofgastric content and producing a floating layerof resin beads in contrast to the uncoatedbeads, which will sink quickly.[15]

7. Osmotic regulated systems

It is comprised of an osmotic pressurecontrolled drug delivery device and aninflatable floating support in a bioerodiblecapsule. In the stomach the capsule quicklydisintegrates to release the intragastricosmotically controlled drug delivery device.The inflatable support inside forms adeformable hollow polymeric bag that containsa liquid that gasifies at body temperature toinflate the bag. The osmotic controlled drugdelivery device consists of two components –drug reservoir compartment and osmoticallyactive compartment.[16]

Polymers Used In Hollow Microspheres

A number of different substances bothbiodegradable as well as nonbiodegradablehave been investigated for the preparation ofmicrospheres; these materials includepolymers of natural origin or synthetic originand also semisynthetic substances. Microspheres can be prepared by using bothhydrophilic and hydrophobic polymers.[17]

• Hydrophilic polymers

These are includes gelatin, agar, egg albumin,starch, chitosan, cellulose derivatives; HPMC, DEAE cellulose.[18]

• Hydrophobic polymers

These are include ethyl cellulose, polylacticacid, PMMA, acrylic acid esters etc.

• Biodegradable polymers

These materials also slowly disappear fromthe site of administration; however it occurs inresponse to a chemical reaction such ashydrolysis.

Example: Polylactic acid (PLA), poly glycolicacid (PGA), Polycaprolactone (PCL) and several generic classes such as the polyanhydrides and poly orthoesters.

• Non-Biodegradable Hydrophobic Polymers
These materials are inert in the environment ofuse, are eliminated or extracted intact from thesite of administration. Example: Polyethylene vinyl acetate (EVA), Polydimethyl siloxane (PDS), Polyetherurethane (PEU), Ethyl cellulose (EC), Cellulose acetate (CA), Polyethylene (PE) andPolyvinyl chloride (PVC), Acrycoat, Eudragit Setc.[19]

• Hydrogels
Hydrogels are polymeric networks based on hydrophilic macromonomers that are able to retain large amounts of water. These polymers swell but do not dissolvewhen brought in contact with water. As withthe hydrophobic polymers, hydrogels are inert, removed intact from the site of administration, and function by forming a rate limiting barrierto the transport and release of drugs.
Example: Polyhydroxy ethyl methyl acrylate (PHEMA), cross-linked poly vinyl alcohol (PVA), cross linked poly vinyl pyrrolidone (PVP), poly acryl amide etc.

• Soluble polymers
These are moderate molecular weight (lessthan 75,000 Daltons) uncross linked polymersthat dissolve in water. The rate of dissolutiondecreases with increasing molecular weight. These materials can be used alone or incombination with hydrophobic polymers toprovide devices that slowly erode over time.

Example: polyethylene glycol (PEG), uncrosslinked poly vinyl alcohol or poly vinylpyrrolidone, hydroxyl propyl methyl cellulose(Methocel) and copolymers of methacrylic acidand acrylic acid methyl ester (Eudragit L) etc.[20]

METHODS OF PREPARATION OF MICROSPHERES

Choosing the method depends primarily on Character of a polymer been using, the drug, the factors equivocally determined by many formulations and technological factors as the size of the particles requirement, and the drug or protein should not be significantly impacted by the process, the reproducibility of the release profile and the method, there should be no stability Issue, in relation to the finished product. The various types of procedures used to prepare the microspheres using hydrophobic and hydrophilic polymers as matrix materials.[11]
• The capacity to integrate medication doses which are relatively small.
• Stability of preparationafter synthesis with a shelf spam which is clinically acceptable.
• Controlled particle size and dispersibility for injection in the aqueous vehicles.
• Effective reagent release with strong control over a large timescale.
• Biocompatibility of controllable biodegradability and chemical alteration response.

1. Wax coating and hot melt

Wax used to encapsulate the main components, by dissolving or dispersing the product in melted wax. The waxy paste or mixture, such as frozen liquid paraffin, released by high intensity blending with cold water. The water is heated up for at least an hour. The substance is stirred up for at least 1 hour. Then the external layer (liquid paraffin) is decanted and the microspheres are immersed in a non-miscible solvent and dry air is required to dry. For the surface ingredients, carnauba wax and beeswax can be used and both should be combined to obtain desirable characteristics.[14]

2. Spray drying technique

This was used to prepare polymer microsphere mixed charged with drug. This requires dispersing the raw substance into liquefied coating liquid, and then spraying the mixture into the air for surface solidification accompanied by rapid solvent evaporation. Organic solvent and polymer solution are formulated and sprayed in various weight ratios and drug in specific laboratory conditions producing microspheres filled with medications. This is fast but may lose crystallinity due to rapid drying.[16]

3. Coacervation

This method is a straight forward separation of macromolecular fluid into two immiscible types of material, a thick coacervate layer, comparatively condensed in macromolecules, and a distilled layer of equilibria. This method is referred to as basic coacervation, in the presence of just one macromolecule. If two or more opposite-charge macromolecules are involved, they are considered complex coacervation. The former iscaused by specific factors including temperature shift, Using non-solvent or micro-ions contributing to dehydration in macromolecules, since they facilitate interactions between polymer and polymer through polymer solvent interactions. This can be engineered to generate different properties on microsphere.[17]

4. Solvent evaporation

The method of solvent evaporation has also been extensively used to preparation of PLA and PLGA microspheres which contain many various drugs. Several variables were identified that can significantly affect microspheric characteristics, such as solubility of drug, internal morphology, type of solvent, diffusion rate, temperature, polymer composition as well as viscosity, and drug loading. The efficacy of the solvent evaporation system to create microspheres relies on the effective entanglement of the active substance into the particles, and therefore this procedure is particularly efficient with drugs that are either insoluble or partially soluble in the liquid medium that constitutes the constant phase.[18]

5. Precipitation

It is a modification of the form of evaporation. The emulsion is polar droplets scattered over a non-polar medium. The use of a co-solvent can extract solvent from the droplets. The subsequent rise in the concentration of polymers induces precipitation to create a micro spheric suspension.[19]

6. Freeze Drying

Freeze-drying is effectively used in protein API microspheres praparation. The method is freezing, sublimation, main drying, and secondary drying. At the freezing step, account is taken of the eutectic point of the components. During the process, lyoprotectants or cryoprotectants will stabilise API molecules by removing water, creating a glass matrix, lowering intermolecular interaction by forming hydrogen bonds between the molecules or dipole - dipole interactions. It's a beneficial cycle for heat tolerant molecules, given its high expense. Freeze-drying produces solidification and then enables the reconstitution of particles in an aqueous media.[20]

7. Single Emulsion Solvent Evaporation Technique

This process requires polymer dissolution in an organic solvent accompanied by emulsification of an aqueous environment containing the emulsifying agent. The resulting emulsion is stirred for several hours in atmospheric conditions to allow the solvent to evaporate, which is then washed, rinsed and dried in desiccators. Designed and manufactured drugs microspheres with polymers by diffusion-evaporation method with emulsion solvent.[3]

8. Double emulsification method

The Doppel-emulsion strategy requires mixing w / o / w or o / w / o processing the double emulsion. The aqueous solution of the product is distributed in a continuous lipophilic organic phase. The continuous step which consists of a polymer solution eventually encapsulates medication Observed in the scattered aqueous layer to form primary emulsion. Prior to introduction to the aqueous solution of alcohol to form primary emulsion, the pre-formed emulsion is subjected to homogenisation or sonication. The microspheres filled with the drug prolonged the release of the medication 24 hours and were Observed to be diffusion and erosion regulated.[8]

9. Ionic gelation method

Ionotropic gelation is depend on the tendency of polyelectrolytes to cross connect to develop hydrogel beads often called gelispheres in the existence of counter ions. Gelispheres are Circular cross linked polymeric hydrophilic agent capable of substantial gelation and thickening in model biological fluids and drug release regulated by polymer relaxation via it. The hydrogelbeads are formed by dumping a drug-laden polymeric solution into the polyvalent cations aqueous solution. The cations migrate through the drug-laden hydrophilic compounds, creating a three-dimensional lattice the moiety is ionically crosslinked. Biomolecules may also be placed into these gel spheres to maintain their three-dimensional form under moderate conditions.[9]

MECHANISM OF FLOTATION OFMICROSPHERES

When microspheres come in contact withgastric fluid, the gel formers, polysaccharides, and polymers hydrate to form a colloidal gelbarrier that controls the rate of fluid penetrationinto thedevice and consequent drug release. As the exterior surface of the dosage formdissolves, the gel layer is maintained by thehydration of the adjacent hydrocolloid layer. The air trapped by the swollen polymer lowersthe density and confers buoyancy to themicrospheres. However a minimal gastriccontent is needed to allow proper achievementof buoyancy.[11]

Mechanism of drug release from themicrospheres

The mechanism of drug release frommultiparticulates can occur in the followingways.

Diffusion

On contact with aqueous fluids in thegastrointestinal tract (GIT), water diffuses intothe interior of the particle. Drug dissolutionoccurs and the drug solutions diffuse acrossthe release coat to the exterior.[8]

Erosion

Some coatings can be designed to erodegradually with time, thereby releasing the drugcontained within the particle.

Osmosis

In allowing water to enter under the rightcircumstances, an osmotic pressure can bebuilt up within the interior of the particle. Thedrug is forced out of the particle into theexterior through the coating.[9]

CHARACTERIZATION OF FLOATING MICROSPHERES

Hollow microspheres are evaluated by their micromeritic properties for instance tappeddensity, compressibility index, particle size, true density and flow properties etc.

1. Micromeritics

Microspheres were characterized for their micromeritics properties such as particle size, angle of repose, compressibility index and Hausner‟s ratio.[6]

A. **Particle size**

The particle size of the microspheres was measured using an optical microscopic method and mean microsphere size was calculated by measuring 200-300 particles with the help of a calibrated ocular micrometer.

Different sizes of microspheres and their distribution in each batch are measured by sieving in a mechanical shaker, using a nest of standard sieves (ASTM) and the shaking period of 15 minutes. Particle size distribution is

found out and the average particle size of hollow microspheres is calculated by means of the following formula.[8]

Mean particle size = Σ (mean particle size of the fraction × weight fraction)/Σ (weightfraction)

B. Bulk density

Bulk density is defined as the mass of powder divided by bulk volume. Accurately weighed 10gm sample of granules was placed into 25 ml measuring cylinder. Volume occupied by the granules was noted without disturbing the cylinder and the bulk density was calculated usingthe equation (values expressed in gm/cm^3).[7]

Bulk density =Weight of sample/Volume of sample

C. Tapped density

Accurately weighed 10 gm of powder sample was placed in 25 ml measuring cylinder. The cylinder was dropped at 2-second intervals onto a hard wooden surface 100 times, from a height of one inch. The final volume was recorded and the tapped density was calculated by the following equation (values expressed in gm/cm^3).[9]

Tapped density=mass of microsphere/volume of microsphere after tapping

D. Carr's index (%)

The Carr‟s index is frequently used as an indication of the flowability of a powder. A Carr index greater than 25% is considered to be an indication of poor flowability and below 15%of good flowability. Flow property of blend depends upon Compressibility index. The Carr‟s index is an indication of the compressibility of a powder. It is calculated by the formula.[11]

Carr′s index (%) = [(Tapped density − Bulk density)/ Tapped density] × 100

E. Angle of repose (θ)

The angle of repose is indicative of flowability of the substance. Funnel was adjusted in such a way that the stem of the funnel lies 2.5 cm above the horizontal surface. The sample powder was allowed to flow from the funnel, so the height of the pile just touched the tip of the funnel. The diameter of the pile was determined by drawing a boundary along the circumference of the pile and taking the average of three diameters.[12]

The angle of repose iscalculated by

θ = tan-1 h/r

Where, θ is angle of repose, h is height of the pile; r is the radius of the pile.

F. Hausner's ratio

The Hausner‟s ratio is an indication of the compressibility of a powder. It is calculated by the formula,

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

The Hausner‟s ratio is frequently used as an indication of the flowability of a powder. AHausner‟s ratio greater than 1.25 is considered to be an indication of poor flowability. Theobservations for the flow properties determinations were recorded.[16]

2. Percentage yield

Percentage yield of buoyant microspheres was calculated by dividing actual mass of product to total amount of all non-volatile components that are used in the preparation of floating microspheres and is represented by following formula.[18]

% yield = (actual weight of floating microspheres / weight of drug taken + total polymer weight) ×100

3. Drug entrapment efficiency (DEE)

The quantity of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance is measured by spectrophotometer against appropriate blank.[15] The amount of drug entrapped in the microspheres was calculated by the following formula.

DEE = (amount of drug actually present/theoretical drug load expected) × 100

4. Surface Morphological Study using SEM

The external and internal morphology of the microspheres are studied by scanning electron microscopy (SEM).[15]

5. In vitro Buoyancy/ Floating behaviour

Floating behaviour of microspheres was studied using a USP dissolution test apparatus II, specified in the USP I. Fifty milligrams of the microspheres are spread over the surface of the dispersing medium (900 ml of 0.1 N HCl) containing 0.02% Tween 80 as surfactant. The dissolution medium was agitated with a paddle rotating at 100 rpm and maintained at 37°C.

After 12 hours, both the floating and the settled portions of microspheres were collected separately. The microspheres were filtered, dried and weighed.[19] The percentage of floating microspheres was calculated using the following equation,

Percentage Buoyancy = Wf / Wf + Ws

Where, Wf and Ws are the masses of the floating and settled microparticles.

6. Dissolution test (in vitro-drug release) of microspheres

The In vitro release rate of floating microspheres was determined in a United States, Pharmacopoeia (USP) I basket type dissolution apparatus. A known quantity of floatingmicrospheres equivalent to the drug dose was filled into a hard gelatin capsule and placed inthe basket of dissolution rate apparatus. 900 ml of the dissolution medium was used andstirred at 100 rpm at 37 ± 0.5 ºC. Samples are withdrawn at a specified time interval

andanalysed by any suitable analytical method, such as UV spectroscopy.[15]

7. *In-vivo* Studies

In vivo studies are generally conducted in healthy male albino rabbits weighing 2-2.5 kg. Theanimals are fasted for 24 hours before the experiments; however, they are given free access tofood and water during the experiments. Blood samples (2 mL) are collected from themarginal ear vein into heparinized centrifuge at an appropriate time interval. The in-vivoplasma summary can be obtained by performing the study in suitable animal models (e.g.beagle dogs). The in-vivo floating behaviour can be investigated by X-ray photography offloating microspheres loaded with barium sulphate in the stomach of beagle dogs. In vivostudies have been also carried out in healthy human volunteers. The pharmacokinetic parameters were determined by the analysis of urinary excretion data.[19]

8. Stability Studies

Optimized formulation was sealed in aluminium packaging, coated inside with polyethylene. The samples were kept in the stability chamber maintained at 40°C and 75% RH for 3months. At the end of studies, samples were analysed for the physical appearance and drugcontent.[20]

CONCLUSION

Drug absorption in the gastrointestinal tract isa highly variable procedure and prolonginggastric retention of the dosage form extends, the time for drug absorption. Hollowmicrosphere promises to be a potentialapproach for gastric retention. Although thereare number of difficulties to be worked out to, achieve prolonged gastric retention, a largenumber of companies are focusing towardcommercializing this technique.

REFERENCES

1. Rajurkar RM, Rathod CP, Thonte SS,Sugave RV, Sugave BK, Phadtare AAand Bhosale PH. GastroretentiveMucoadhesive Microsphere as Carriers in Drug Delivery: A Review. Indo American Journal of Pharm Research, 2013; 3(3): 2751-2777.
2. GÜNEŞM, KARAVANA SY, ALGIN YAPARE. Buccal drug delivery system: an overview about dosage forms and recent studies. Universal Journal of Pharmaceutical Research, 2019; 4(6): 69-74.
3. Satish V. Shirolkar, Mukund.G.tawar, Nishant. S. Gandhi and Nilesh B. Development and Evaluation of Floating Microspheres of Pioglitazone Hydrochloride Using Ethyl Cellulose. Der Pharmacia Lettre, 2010; 2(5): 261-277.
4. Igwe J. Chibueze, Emenike IV, Oduola AR. Formulation and evaluation of Finasteride sustained-release matrix tablets using different rate controlling polymers. Universal Journal of Pharmaceutical Research, 2016; 1(2): 15-18.
5. Kapil K and Rai AK. FloatingMicrosphere: An innovative Approachfor Gastro Retention. Journal of Pharmacy Reasearch, 2012; 5(2): 883-886.
6. Andrew EC, Grace EA, Salome CA, Elochukwu A, Izuchukwu BC, Ejiofor UK, Lorrita CC, Godswill O. Evaluation of Metronidazole tablets formulated with different disintegrants usingmoisture activated dry granulation. Universal Journal of Pharmaceutical Research, 2023; 8(3): 34-39.
7. Singh B, Kanouji J, Pandey M andSaraf SA. Formulation and Evaluationof Floating Microspheres ofFamotidine. International Journal ofPharmtech Research, 2010; 2(2): 1415-1420.
8. Opeyemi OT, Adegbenro OO. Development and characterization of direct compressed matrix mini tablets of naproxen sodium. Universal Journal of Pharmaceutical Research, 2018; 3(5): 63-68.
9. Monica K, Upendra J and Jaspreet R.Recent Advances in Floating Microspheres as Gastro-Retentive Drug Delivery System: A Review. IntRecent Adv Pharm Res, 2012; 3(2): 5-23.
10. Shaikh SC, Sanap D, Bhusari DV, Jain S, Kochar PP, Sanchati VN. Formulation and evaluation of Ibuprofen gastro-retentive floating tablets. Universal Journal of Pharmaceutical Research, 2018; 3(4): 19-23.
11. Kunal PN, Pratik U, Jayanth DAR.Valera and Nirav PC. Gastroretentive Drug Delivery Systems and RecentApproaches: A Review. JPRO, 2012; 2(1): 1-8.
12. Ikechukwu UR, John Francis DE, Ambi AA. Development and evaluation of Ritonavir hollow microballoons for floating drug delivery. Universal Journal of Pharmaceutical Research, 2017; 2(2): 8-11.
13. Jagtap YM, Bhujbal RK and RanpiseNS. Floating Microsphere: A Review. BJPS, 2012; 4(1): 17-30.
14. Anyanwu NCJ, Adogo LY, Ajide B. Development and evaluation of in situ gelling gastroretentive formulations of Meloxicam. Universal Journal of Pharmaceutical Research, 2017; 2(3): 10-13.
15. Sattinderkakar, Ramandeep S andShallusandan. Gastro retentive DrugDelivery Systems: A review. Afr. J.Pharm. Pharmacol. 2015; 9(12): 405-417.
16. Yusuf FS. Formulation and in-vitro evaluation of floating microballoons of stavudine. Universal Journal of Pharmaceutical Research 2016; 1(1): 8-11.
17. Dutta P, Sruthi J, Niranajan Patra Chand Bhanoji R. Floating Microspheres: Recent Trends in the Development of Gastroretentive Floating DrugDelivery System. International Journal of Pharmaceutical Sciences and Nanotechnology, 2011; 4(1): 1296-1306.
18. Kaur G, Paliwal S. Formulation and evaluation of etoricoxib microbeads for sustained drug delivery. Universal Journal of Pharmaceutical Research, 2019; 4(1): 35-39.
19. Deepak A, Dighe, Naresh H, Choudhary, Mangesh ST, Prasad RV, Manoj SK and Meera CS. Floating Drug Delivery System: A NovelApproach towards Gastro retention. International Journal of

Pharmaceutical and Chemical Sciences, 2012; 1(3): 1128-1142.
20. Agarwal P, Semimul A. A comprehensive review on sustained release matrix tablets: a promising dosage form. Universal Journal of Pharmaceutical Research, 2018; 3(6): 49-54.