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A Review On Gastroretentive Floating Beads

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ABSTRACT

Gastroretentive delivery systems can be retained in the stomach and assist in improving absorption and consequently the bioavailability of drug that has a narrow absorption window in a particular region of gastrointestinal tract. Floating beads are often having gastro retentive property without affecting the gastric emptying rate they are used for controlled drug release. Floating beads drug delivery systems are mainly based on non-effervescent system. Floating beads is useful for various categories of drugs which act locally in stomach, poorly soluble in alkaline pH, having narrow absorption window, unstable in intestine or colonic environment and primarily absorbed in stomach. In this review types, method of preparations, evaluation techniques, advantages, limitation and applications of floating beads are discussed.

KEYWORDS: Floating dosage form, floating beads, Gastroretention.

INTRODUCTION:

The Oral route is most convenient and extensively used dosages form. Primarily due to ease of administration this route has high patient acceptability [1-4]. The goal of any drug delivery system is to maintain the desired drug concentration by releasing a therapeutic amount of drug to the specific site in the body [5]. Gastric emptying is a complex process that is highly variable and makes the in vivo performance of drug delivery systems. All these physiological problems are overcome by drug delivery systems with prolonged gastric retention time. Gastro retentive drug delivery is an approach to enhance gastric residence time, thereby targeting to a specific site and shows local or systemic effects. Floating systems or hydro dynamically controlled systems are low density systems which have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. [6] While the particulate is floating in the gastric content; the drug is released slowly from the particulate at a desired rate. Carbon dioxide gas forming agents such as carbonates or bicarbonates are commonly used as material in FDDS.

APPROACHES FOR GASTRO RETENTION

Effervescent systems

- Volatile liquid containing systems
- Gas-generating Systems

Non-effervescent systems

- Colloidal gel barrier systems
- Micro-porous Compartment System
- Hollow microspheres

• Mucoadhesive systems

Effervescent system

It is a matrix type of system prepared with the help of swellable polymer such as methylcellulose and Chitosan and other effervescent compounds. Example: sodium bicarbonate, tartaric acid, citric acid. These are formulated in such a way that when they come in contact with gastric content, CO2 is liberated and gets entrapped in swollen hydrocolloid which provides buoyancy to dosage form and making it float over a time.

a) Gas generating system:

These buoyant systems utilize effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid. The system is so prepared which upon arrival in the stomach, carbon dioxide is released, results in the formulation to float in the stomach. Other materials have been reported like mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that release carbon dioxide when ingested.[9]

b) Volatile liquid containing system:

By incorporating an inflatable chamber which contains a liquid, the GRT of a drug delivery system can be sustained. e.g., ether, cyclopentane, at body temperature it gasifies resulting the inflatation of the chamber in the stomach. A bio erodible plug is present in that device which is made up of PVA, Polyethylene, etc. that slowly dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.[22]

Non effervescent system

Non-Effervescent FDDS use a gel forming (or) swellable cellulose type of hydrocolloids, formulation which can be done by mixing of the drug with gel forming hydrocolloids which swell in contact with gastric fluid after oral administration and maintains integrity of shape and a bulk density barrier, the air trapped by swollen polymer results in buoyancy to the dosage forms. They are classified into –

a) Colloidal gel barrier systems

b) Microporous Compartment systems

c) Alginate beads

d) Hollow microspheres

a) Colloidal gel barrier system:

This system contains drug with gel-forming hydrocolloids which remain buoyant on the stomach contents. This increases GI residence time and enhances drug reaching to absorption site in the solution form which is ready for absorption. In contact with gastric fluid, in the system the hydrocolloid hydrates forms a colloidal gel barrier around its surface. The formed colloidal gel barrier controls the rate of fluid penetration into the device and followed by release of the drug. [8]

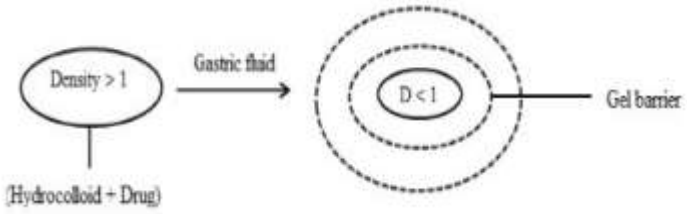

Fig 1: Colloidal gel barrier system

a) Microporous Compartment systems:

This system is based on the encapsulation of a drug reservoir inside a Microporous compartment with aperture along its top and bottom walls. The drug reservoir presents in compartment and its peripheral wall is completely sealed to prevent direct contact of gastricmucosal surface with the undissolved drug. In the stomach entrapped air present in the floatation chamber causing the delivery system to float over the gastric content. Gastric fluid enters through the pores, dissolves the drug and carrier, the dissolved drug for continuous transport across the intestine for absorption. [7]

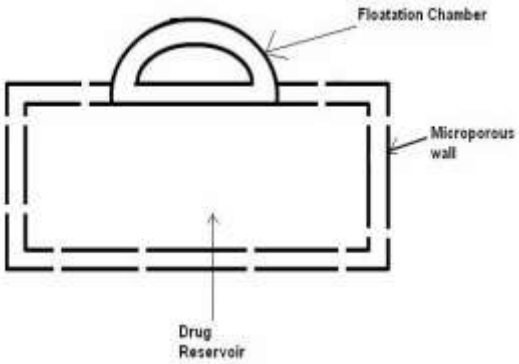

Fig 2: Microporous Compartment systems

b) Alginate beads:

Multi-unit floating dosage forms prepared from freeze-dried calcium alginate by dropping sodium alginate solution into calcium chloride aqueous solution were spherical beads of approx. 2.5 mm in diameter can be prepared beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -400C for 24 hours, resulting in the formation of a porous system, which can float for over 12 hours. These floating beads give an enhanced residence time of more than 5.5 hours. [9]

c) Hollow microspheres:

Hollow microspheres carried with drug in their outer polymer shelf which is prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 400C. The gas phase is formed in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. Floating of micro balloon continuously over the surface of an acidic dissolution media for more than 12 h which containing surfactant.[9]

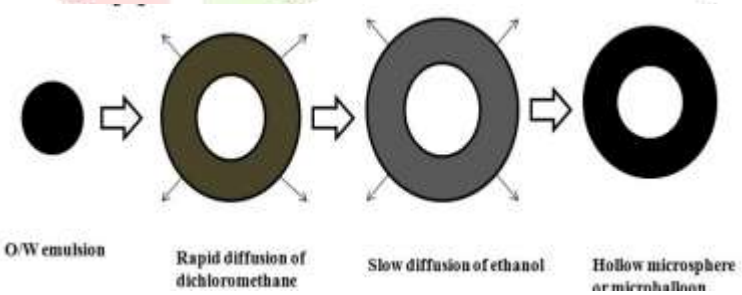

Fig 3: Formulation of floating hollow microsphere or microballoon

ADVANTAGES

1. Improves patient compliance.
2. Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release.
3. Freedom from incompatibilities between drug and excipients especially with buffers.
4. Better therapeutic effect of short half-life drugs can be achieved.
5. Gastric retention time is increased because of buoyancy.
6. Site specific drug delivery to the stomach can be achieved.
7. Mask the unpleasant odour, taste of drugs and protect the drugs from the environment.

8. Freedom from incompatibilities between drugs and excipients especially the buffers and safe handling of toxic substances.
9. Pulsatile release of antibiotics can alleviate evolution of the bacterial resistance. In the vaccine delivery, initial burst followed by delayed release pulses can mimic initial and boost injection, respectively.
10. The local delivery system avoids systemic drug administration for local therapeutic effects and can reduce the related systemic side effects.
11. The volatile drugs can be easily formulated as floating microspheres compared to other conventional dosage forms.

DISADVANTAGES

1. These systems require a high level of fluid in the stomach for drug delivery to float however this can be overcome by using low density polymers.
2. The release rate of the controlled release dosage form varies from a variety of factors like rate of food transit through the drug.
3. Potential toxicity due to loss of integrity of drugs.
4. The dosage forms should be administered with more amount of water (200-250ml).
5. Some drugs present in the floating system causes irritation to gastric mucosa.
6. These dosage forms should not be crushed or chewed.

FACTORS AFFECTING GASTRIC RETENTION

1. Density of dosage form: Density o gastric fluid is reported to be 1.004gm/ml. The density of the dosage form should be less than this for buoyancy, so that it is retained in the stomach for a longer time. Dosage forms may have a high density in the beginning but float in the stomach due to reduction in density by swelling.[10]
2. Composition of meal: Fats, particularly fatty acids inhibit gastric secretion and have a pronounced reductive effect on the rate of emptying. Proteins and starch are shown to have inhibitory effect on gastric emptying, though to a less extent. As the viscosity of the gastric fluids is increased, there is a corresponding decrease in the rate of emptying.
3. Caloric content: Gastric residence time can be increased by 4-10 hrs with a meal that is rich in proteins and fats.
4. Frequency of the food: -The gastric residence time can increase by >6 hrs when successive meals are given, compared with a single meal, due to low frequency MMC.
5. Size of dosage form: -In general it is known that indigestible solids > 1-2mm are retained in the stomach throughout the postprandial period, after which they are emptied by cyclical recurring burst of inter digestive gastric contractions. Many recent studies have shown that non disintegrating tablets as large as 7.0mm can be emptied from the human stomach during the postprandial period, while 13.0mm tablets are retained until arrival of subsequent sweeping 'housekeeper waves. This emphasizes the need for size enlargement of dosage forms in the stomach in order to prolong the gastric residence time.[11]
6. Sex: -Generally females have a slower gastric emptying rate (4.6 1.2hrs) than males (3.40.6hr) regardless of weight, height and body surface area.
7. Body posture: -Gastric emptying is favoured while standing and by lying on the right side since the normal curvature of the stomach provides a downhill path whereas lying on the left side or in supine position retards it.
8. Emotional state of subject: -The influence of emotional factors on gastric motility depending upon whether the emotional experience is of an aggressive or a depressive type.
9. Effect of drugs: -Drug that retard gastric emptying includes poorly soluble antacids (Aluminium hydroxide), anticholinergics (Atropine, Propantheline), narcotic analgesics (Morphine) and tricyclic antidepressants (Imipramine, amitriptyline), Metoclopramide, domperidom and cisapride (Anti emetics) stimulates gastric emptying.
10. Exercise: Vigorous physical activity retards gastric emptying.

11. Disease states: Diseases like gastroenteritis gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastric emptying. Duodenal ulcer and hyperthyroidism promote gastric emptying rate.
12. Gastrointestinal pH: Gastric emptying is retarded at low stomach pH and promoted at higher or alkaline ph. Chemicals that affect gastrointestinal pH also alter gastric emptying. The inhibitory effect of various acids on gastric emptying decreases with increase in molecular weight and is in the following order HCL>Acetic>lactic>tartaric>citric. With alkaline solutions, a low base concentration (1% NaHCO3) increases the gastric emptying rate more than the1 of higher concentration (5%).

DRUGS SUITABLE FOR GRDDS

1. Drugs acting locally in the stomach. E.g. Antacids and drugs for H. Pylori viz., Misoprostol
2. Drugs that are primarily absorbed in the stomach. E.g., Amoxicillin
3. Drugs that is poorly soluble at alkaline ph. E.g., Furosemide, Diazepam, Verapamil
4. Drugs with a narrow window of absorption. E.g., Cyclosporine, Methotrexate, Levodopa, etc.
5. Drugs which are absorbed rapidly from the GI tract. E.g., Metronidazole, tetracycline.
6. Drugs that degrade in the colon. E.g. Ranitidine, Metformin HCl.
7. Drugs that disturb normal colonic microbes. E.g., antibiotics against Helicobacter pylori

DRUGS UNSUITABLE FOR GRDDS

1. Drugs that have very limited acid solubility. E.g., phenytoin etc.
2. Drugs that suffer instability in the gastric environment. E.g. Erythromycin etc.
3. Drugs intended for selective release in the colon. E.g. 5-amino salicylic acid and corticosteroids etc.

ROLE OF POLYMERS IN FLOATING DRUG DELIVERY

The currently available polymer-mediated non effervescent and effervescent FDDS, designed on the basis of delayed gastric emptying and buoyancy principles, appear to be an effective and rational approach to the modulation of controlled oral drug delivery. This is evident from the number of commercial products and a myriad of patents issued in this field. The FDDS become an additional advantage for drugs that are absorbed primarily in the upper segments of GI tract, i.e., the stomach, duodenum and jejunum. Some of the unresolved, critical issues related to the rational development of FDDS include: -

(1) The quantitative efficiency of FDDSs in the fasted and fed states;

(2) The role of buoyancy in enhancing GRT of FDDS; and

(3) The correlation between prolonged GRT and SR/PK characteristics.

FLOATING BEADS CAN BE PREPARED BY

Solvent evaporation method

Floating multi particulate dosage form was prepared by solvent diffusion and evaporation methods to create the hollow inner core. The polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing polyvinyl alcohol to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the temperature under pressure or by continuous stirring. The solvent removal leads to polymer precipitation at the o/w interface of droplets, forming cavity and thus making them hollow to impart the floating properties. The polymers studied for the development of such systems include Cellulose acetate, Chitosan, Eudragit, Acrycoat, Methocil, Polyacrylates, Polyvinyl acetate, Carbopol, Agar, Polyethylene oxide and Polycarbonates [12]. Furthermore, a novel multi-particulate gastro-retentive drug delivery system based on low-density foam powder has been proposed and its performance demonstrated in and Floating micro particles consisting of Polypropylene foam powder, Verapamil HCl (as the model drug) and Eudragit RS, Ethyl cellulose or Poly (methyl methacrylate) (PMMA) were prepared with an oil-in-water solvent extraction/evaporation method. The drug and release-rate-controlling polymer were dissolved in Methylene chloride. Polypropylene foam powder was then dispersed within this organic

phase. The resulting suspension was subsequently emulsified into an external aqueous Poly (vinyl alcohol) solution and agitated with a stirrer to allow microparticle formation. The microparticles were separated by being sieved, washed with water and dried in a desiccator; they were irregular in shape and highly porous. Importantly, the drug encapsulation efficiency was high and almost independent of the theoretical loading of the system. In all cases, good in-and floating behaviour was observed. Interestingly, a broad spectrum of release patterns could be obtained with the investigated formulations. Further studies focused on the development of an improved preparation method for this type of low density, foam-based, floating micro-particle and also on the demonstration of the system's performances.

Emulsion Gelation Method

In this method the polymer is dissolved in distilled water which is kept in a magnetic stirrer. After complete homogenization of polymer required quantity of oil is introduced then followed by drug. The resultant homogenous mixture containing drug, oil and polymer is introduced into 5% calcium chloride through 21G needle, which is left at room temperature. After specific period time the filter the solution, the resultant beads were washed twice through distilled water and dried at room temperature for 12 hrs.

Ionotropic gelation method

The hydrogel beads are prepared by introducing a drug-loaded polymeric solution into the aqueous solution of polyvalent cations through the 21G needle. The cations tend to diffuse into the drug-loaded polymeric drops, resulting in the formation of a three dimensional lattice of ionically crosslinked moiety. These beads are then dropped in aqueous solution of 1% glutaraldehyde for about 1h. Biomolecules can also be loaded into these gelispheres under mild conditions to retain their three-dimensional structure. Beads are dried in an air convection type oven at 40°C for 6 h and in freeze dryer to evaluate the changes in beads.

EVALUATION TESTS FOR FLOATING BEADS

Angle of Repose

Angle of repose helps to evaluate powder flowability by assessing inter particulate friction. In general, the higher is the angle of repose poor is the flowability of powder [13]. The angle of repose of each powder blend was determined by glass funnel method, using following equation,

$$tan\theta = \frac{h}{r}$$

Where, θ-angle of repose, h -height of pile above the flat surface, r -radius of the circle formed by the powder blend.

Bulk Density

It is ratio of mass to bulk volume. Bulk density may influence dissolution and other properties and depends on the particle size, shape and tendency of particles to adhere together. Bulk density of formulated beads was determined by taking a known mass of beads in a 5 ml graduated measuring cylinder. The cylinder was dropped three times from a height of one inch at an interval of two seconds. The bulk density was calculated by following equation

$$Bulk\ density = \frac{Mass\ of\ beads}{Bulk\ volume}$$

Tapped density

Tapped density helps to determine packing geometry and flowability. Tapped density is the volume of powder determined by tapping using measuring cylinder containing weighed amount of sample. Tapped density of beads was calculated by following equation,

$$Tapped\ density = \frac{Mass\ of\ beads}{Volume\ of\ beads\ after\ tapping}$$

Carr's compressibility index

This is an important property in maintaining uniform weight. It is calculated using following Equation,

$$Carr's\ index = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

Hausner's ratio

Hausner's ratio less than1.25 indicates good flow and greater than 1.5 indicates poor flow whereas between 1.25 and 1.5 indicates glidant normally improves flow. Hausner's ratio can be calculated by formula

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

Morphology study

Scanning Electron Microscopy (SEM) was performed to characterize the surface of formed beads. Beads were mounted directly onto the sample stub and coated with gold ion and analyse for surface morphology.

Particle size analysis

The particle size of drug loaded formulations were measured by an optical microscope fitted with calibrated ocular and stage micro meter and particle size distribution was calculated. 50 particles in five different fields were examined.

Determination of Percentage yield

The prepared beads were collected and weighed. The measured weight was divided by the total amount of all non-volatile components, which were used for the preparation of the beads.

$$Percentage\ yield = \frac{Actual\ weight\ of\ products}{Weight\ of\ drug\ and\ excipients} \times 100$$

Drug Entrapment Efficiency

Beads equivalent to 100 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the beads 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 [14]. The solution was filtered and the absorbance was measured at suitable wavelength against appropriate blank. The amount of drug entrapped in the beads was calculated by the following formula,

$$Entrapment\ efficiency = \frac{Actual\ yield}{Theoretical\ yield} \times 100$$

In vitro buoyancy study

Beads (300mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 ml of 0.1 N HCl containing 0.02% Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 hr. The floating and the settled portions of beads were recovered separately. The beads were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the beads that remained floating and the total mass of the beads.[15]

$$\%Buoyancy = \frac{Qf}{Qf+Qs} \times 100$$

Where, Qf= Weight of the floating Beads Qs = Weight of settled Beads

In-vitro drug release study

The drug release study from beads is performed using USP dissolution apparatus Type I in 900 ml of 0.1 N HCl dissolution media (pH-1.2) at 100 rpm and 37°C. 2 ml sample was withdrawn at 1 hr. time interval for 12 hr. and same volume of fresh medium was replaced to maintained sink condition. Withdrawn samples were assayed spectrophotometrically at suitable wavelength. The drug release was analysed by UV Spectro-photometer.

Determination of Moisture Content

The formulations were subjected to moisture content study by using an IR moisture balance by placing the beads at 60°C for 10 min.

APPLICATION OF FLOATING DRUG DELIVERY SYSTEMS [16]

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows:

1. Sustained drug delivery
   FDDS can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited. E.g., Sustained release floating capsules of Nicardipine Hydrochloride.
2. Site-specific drug delivery
   These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine. E.g., Riboflavin and Furosemide.
3. Absorption enhancement
   Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.
4. Reduced fluctuations of drug concentration
   Continuous input of the drug following Controlled Release administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index.
5. Improved selectivity in receptor activation
   Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.
6. Maintenance of Constant Blood Level
   These systems provide an easy way of maintaining constant blood level with an ease of administration and better patient compliance.

CONCLUSION

Based on the review it can be concluded that the floating beads show gastro retentive controlled release property. Floating beads having low-density, adequate buoyancy to float over gastric contents and remain in stomach for longer period of time. As a result, the drug released slowly at desired rate from the system which result in the increased gastric retention with low fluctuations in plasma drug concentration. In future by using various other strategies, floating beads may show the better place in novel drug delivery system, exactly in

diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective in vivo delivery diseased organ and tissues in the body. This will enhance the absorption of drugs by slowly releasing in to the site of absorption. The floating beads exhibit better bioavailability characteristic when compared with commercial conventional drugs.

REFERENCES

[1] Fayaz W, Chasta P, Hassan Sheikh T, Ahmad M, Hussain Kumar A, Mustafa A. 2018. Gastro retentive Drug Delivery System. Journal of Drug Discovery and Development, 2(1):11-17.

[2] Kumar R, Chandra A, Saloni S, 2017.Gautam PK. Advanced multiple unit controlled release floating beads: A review. World J Pharm Res.6: 238-59.

[3] Ghareeb MM, Issa AA, Hussein AA. 2012. Preparation and characterization of cinnarizine floating oil entrapped calcium alginate beads. International Journal of Pharmaceutical Sciences and Research,3(2):501.

[4] Pahwa R, Bhagwan S, Kumar V, Kohli K. 2010. Role of Natural Polymers in The Development of Floating Drug Delivery Systems, Journal of Pharmacy Research ,3(6):1312-1318.

[5] Ganesh N, Bharathi G, Joshi H, Jayanthi C, Singh DP. 2013, Buoyant Multi particulate Drug Delivery – A Focus on Hydrogel Beads, World J Pharm Res, 2(2):450-64.

[6] Archana DK, Chandewar A.V. 2016.Formulation and Evaluation of Oral Floating Beads of Tramadol Hydrochloride, Journal of Drug Delivery&Therapeutics,6(4):7-16.

[7]. Gupta P, Gnanarajan, Kothiyal P. Floating Drug Delivery System, International Journal of Pharma Research & Review, 2015; 4(8):37-44.

[8]. Sahil K, Akanksha M, Sudeep B, Premjeet S. Floating Drug Delivery System, International Research Journal of Pharmacy, 2011;2(9):18-24.

[9]. Garg R, Gupta GD. Progress in Controlled Gastroretentive Delivery Systems, Tropical Journal of Pharmaceutical Research, 2008; 7(3):1055-66.

[10] Timmermans, J., Moes, A.J.1990. How well do floating dosage forms float? Int J Pharm. 62: 207-216.

[11] El-Kamel, A.H., Sokar, M.S., Al Gamal, S.S., Naggar, V.F. 2001. Preparation and evaluation of ketoprofen floating oral delivery system, Int J Pharm. 220(1-2): 13-21. DOI PMid: 11376963.

[12] Nethaji R, Narayanan A, Palanivelu M. 2016.Formulation and Evaluation of metformin hydrochloride loaded mucoadhesive microspheres. Int J Pharma, Chem and Bio Sci. 6(2), 124-132.

[13] KakarS, Singh R, Shallusandhan. 2015. Gastroretentive drug deliverysystems: A review, African J Pharmaand Pharmacology,9(12), 405-417.

[14] Parsekar SD, Prabhu S, Shetty A. 2014.A Brief Review on Floating BilayerTablet as a Convenient Gastro-retentive Drug Delivery System.Int J Pharmal and ChemicalSci., 3(2), 420-430.

[15] El-Gibaly, I. 2002. Development and in vitro evaluation of novel floating chitosan microcapsules for oral use: comparison with non-floating chitosan microspheres, Int. J.Pharm. 249, 7-21.

[16] Verma R, Devre Kishor, Gangrade Tushar, 2014. Bi-layer tablets for various drugs: A review, Scholars Academic J Pharma., 3(3), 271-279.

[17] Kumar K, Pant NC, Ahmad S, Fateh MV, RaiAK, VermaB, ChaurasiaH. 2016. Development and evaluation of floating microspheres of curcumin in alloxan induced diabetic rats, Tropical Journal Pharmaceutical Research., 15 (9), 1819-1825.

[18] Jain P., Jain D. 2017.Development of clarithromycin gastro retentive microspheres. Journal of Drug Delivery and Therapeutics, 7(7):81-83. doi:10.22270/jddtv7i7.1594.

[19] Vedhahari. 2010.The recent developments on gastric floating drug delivery systems: an Overview. Int J Pharm Res. 2(1), 524-534.

[20] GargR, Gupta GD, 2008.Progress in Controlled Gastro retentive Delivery Systems. Trop J Pharma Res, 7 (3): 1055-1066.

[21] KumarK, RaiAK. 2012. Floating Microsphere: An innovative Approach for Gastro retention, Journal of Pharmacy Research.5(2):883-886

[22]. Tripathi P, Ubaidulla U, Kishan Khar R. Floating Drug Delivery System, International Journal of Research And Development In Pharmacy And Life Sciences 2012;1(1):1-10 .