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Recent Trends in Floating Drug Delivery Systems (FDDS) or Hydro dynamically Controlled Systems: A Novel Approach for Solubility

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ABSTRACT
Floating drug delivery systems (FDDS) or hydro dynamically controlled systems are low-density systems that 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. These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO_2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme. Over past 30 year as the expanse and complication involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist. The concept of targeting i.e. site specific drug delivery is a well established dogma, which is gaining full attention. Placement of the particles indiscrete anatomical compartment leads their retention either because of the physical properties of the environment of biophysical interaction of the particles with the cellular content of the target tissue.

KEYWORDS-
Recent Trends, Floating Drug Delivery Systems, Hydro dynamically Controlled Systems, Novel Approach, Solubility, Biophysical Interaction

INTRODUCTION

Floating drug delivery systems (FDDS) or hydro dynamically controlled systems are low-density systems that 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. This results in an increased Gastric retention time and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres.[1]

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM

A. Effervescent system

• Gas generating system
• Volatile liquid containing system

B. Non-effervescent System

• Colloidal gel barrier system.
• Alginate beds.
• Hollow microspheres / Microballons.
• Intragastric Floating Drug Delivery Device / Microporous compartment system[2-5]

A. Effervescent Systems:

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds, e.g., sodium bicarbonate, tartaric acid, and citric acid. [6-8]

a. Volatile liquid containing systems:

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid(like ether, cyclopentane), that gasifies at body temperature cause the inflatation of the chamber in the stomach. [9]

b. Gas-generating Systems:

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonatesalts and citric/tartaric acid to liberate CO_2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme. How the dosage form float is shown in the figure 1. [10-11]

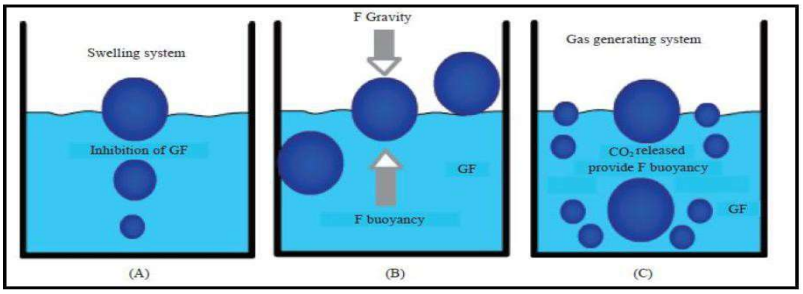

Figure 1: Gas-generating Systems

B. Non-effervescent systems:

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. [12-15]

a. Colloidal gel barrier systems:

Hydro dymamically balance system (HBSTM) was first design by Sheth and Tossounian in 1975.Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids. e.g. HEC, HPMC, NaCMC, Polysacchacarides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. [16]

b. Alginate beads:

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. [17]

c. Hollow microspheres:

Hollow microspheres (microballons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°C. [18-20]

d. Intragastric / Microporous compartment system:

The system composed of a drug reservoir encapsulated in a microporous compartment having pores on top and bottom surfaces. The peripheral walls of the reservoir compartment were completely sealed to prevent any physical contact of the un dissolved drug with walls of the stomach. [21-23]

ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM:

These advantages include:

- ✓ Floating dosage forms such as tablets or capsules will remains in the solution for prolonged time even at the alkaline pH of the intestine.
- ✓ FDDS dosage forms are advantageous in case of vigorous intestinal movement and in diarrhoea to keep the drug in floating condition in stomach to get a relatively better response.
- ✓ Acidic substance like aspirin causes irritation on the stomach wall when come in contact with it hence; HBS/FDDS formulations may be useful for the administration of aspirin and other similar drugs.
- ✓ The FDDS are advantageous for drugs absorbed through the stomach eg: Ferrous salts, Antacids. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site .
- ✓ Controlled delivery of drugs. It minimizes the mucosal irritation by releasing drug slowly.
- ✓ Treatment of gastrointestinal disorders such as gastro esophageal reflux.

DISADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM:

- ✓ Floating system is not feasible for those drugs that have solubility or stability problem in GI tract.
- ✓ These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently coat, water.
- ✓ The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, may not be desirable candidate. E.g. Nifedipine.
- ✓ The ability of drug to remain in the stomach depends upon the subject being positioned upright.
- ✓ The residence time in the stomach depends upon the digestive state. Hence, FDDS should be administered after the meal.
- ✓ Not suitable for drugs that cause gastric lesions e.g. Non steroidal anti inflammatory drugs. Drugs that are unstable in the strong acidic environment, these systems do not offer significant advantages over the conventional dosage forms. [24-27]

MODES OF DRUG DELIVERY

Over past 30 year as the expanse and complication involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exist.

The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting, the goal in designing sustained or controlled delivery system is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action reducing the dose required, or providing uniform drug delivery. [28-30]

This correctly suggests that there are sustain release system that cannot be considered controlled release system. In

general, the goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of drug for an extended period: this is usually accomplished by attempting to obtain zero order release from the dosage form.[31-33]

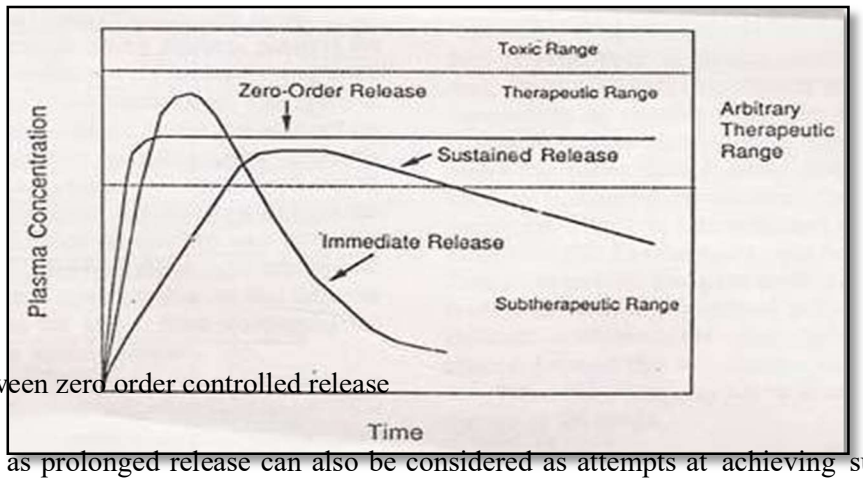

Figure 2: Differences between zero order controlled release

Systems that are designed as prolonged release can also be considered as attempts at achieving sustained release delivery. [34]

The slow first order obtained by a sustained release pre parathion is generally achieved by the release of the drug from a dosage form. In some cases, this achieved by making slow release of drug from a dosage form. In some cases, this is accomplished by a continuous release process. [35, 36]

Factors Affecting Sustained Release Dosage Forms: ***Physicochemical properties of drug***

Dose size

If an oral product has a dose size greater that 0.5 gm it is a poor candidate for sustained release system. Since addition of sustaining dose and possibly the sustaining mechanism will, in most cases generates a substantial volume product that unacceptable large.

Aqueous solubility

Most of drugs are weak acids or bases, since the unchanged form of a drug preferentially permeates across lipid membranes. Aqueous solubility will generally be decreased by conversion to an unchanged form for drugs with low mechanism.

Partition coefficient

Partition coefficient is generally defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Accordingly compounds with relatively high partition coefficient are predominantly lipid soluble and consequently have very low aqueous solubility. Compounds with very low partition coefficients will have difficulty in penetrating membranes resulting poor bioavailability

Pka

The relationship between Pka of compound and absorptive environment, presenting drug in an unchanged form is adventitious for drug permeation but solubility decrease as the drug is in unchanged form.

Drug stability

Orally administered drugs can be subject to both acid base hydrolysis and enzymatic degradation. Degradation will proceed at the reduced rate for drugs in the solid state, for drugs that are unstable in stomach: system that prolong delivery ever the entire course of transiting tried are beneficial.

Molecular size and diffusivity

The ability of drug diffuse through membranes is so called diffusivity and diffusion coefficient is function of molecular size (or molecular weight). Generally, values of diffusion coefficient for intermediate molecular weight drugs, through flexible polymer range from 10-8 being most common for drugs with molecular weight greater than

500, the diffusion coefficient in many polymers frequently are so small that they are difficult to quantify i.e. less than 16-12 cm^2 /sec.

Protein binding

It is well know that many drugs bind to plasma protein with a concomitant influence on the duration of drug action. Since blood proteins are for the most part re- circulate and not eliminated, drug. [12-15]

Biological factors

Biological half life

The usual goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period. To action this, drug must enter in the circulation of approximately the same rate of which it is eliminated. The elimination rate is quantitatively described by half-life ($t_{1/2}$). [12-15]

Absorption

The rate, extent and uniformity of absorption of a drug are important factors when consider its formulation into a sustained release system. As the rate limiting step in drug delivery from a sustained-release system is its release from a dosage form, rather than absorption.

Distribution

The distribution of drugs into tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition.

Metabolism

Drugs that are significantly metabolized before absorption, either in lumen or the tissue of the intestine, can show decreased bioavailability form slower-releasing dosage forms. [12-15]

Strategies and Design of oral controlled release systems

The Design and fabrication of oral controlled release systems is reviewed under the following classification

I. Continuous Release Systems

- Dissolution Controlled release systems
- Diffusion Controlled release systems
- Dissolution and diffusion controlled release systems.
- Ion-Exchange Systems.
- Slow dissolving salts and complexes.
- pH dependent formulations.
- Osmotic pressure controlled release systems.
- Hydrodynamic pressure controlled release systems.

II. Delayed Transit and Continuous release systems

1. Altered density systems.
2. Mucoadhesive systems.
3. Size-based systems.

III. Delayed release systems

Intestinal release systems Colonic release systems.

POLYMER EMPLOYED AS MICROSPHERES

Microsphere used usually are polymers.

They are classified into two types:

1. Synthetic polymers
2. Natural polymers[37]

SYNTHETIC POLYMERS

- Poly methyl methacrylate
- Poly methyl methacrylate copolymer
- Poly methyl cyanoacrylate
- Poly isobutyl cyanoacrylate
- Poly hexyl cyanoacrylate
- Poly acrylamide
- Poly (Na, N-L- lysinediylterephthalamide)
- Poly D, L-lactide
- Poly acryl dextran
- Poly acryl starch
- Poly lactic acid
- Poly lactic acid-poly glycolic acid copolymers
- Ethyl cellulose
- Eudragit RL
- Eudragit RS

NATURAL POLYMERS

- Albumin
- Gelatin
- Collagen
- Agarose
- Carrageenan
- Chitosan
- Starch
- Poly dextran
- Poly starch

PREREQUISITES FOR IDEAL MICROPARTICULATE CARRIERS

The material utilized for the preparation of microparticulates should ideally fulfill the following prerequisites:

- Longer duration of action
- Control of content release of therapeutic efficacy
- Protection of drug
- Reduction of toxicity
- Biocompatibility
- Sterilizability
- Relative stability
- Water solubility or dispersability
- Bioresorbability
- Targetability
- Polyvalent

METHODS OF PREPARATION

1. Preparation of microsphere should satisfy certain criteria:
2. The ability to incorporate reasonably high concentrations of the drug.
3. Stability of the preparation after synthesis with a clinically acceptable shelf life. Controlled particle

size and dispersability in aqueous vehicle for injection.

4. Release of active reagent with a good control over a wide time scale.
5. Biocompatibility with a controllable biodegradability and susceptibility to chemical modification. [37]

SINGLE EMULSION TECHNIQUE

The micro particulate carriers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. [30-33]

DOUBLE EMULSION TECHNIQUE

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to water soluble drugs, peptides, proteins and the vaccines. [30-33]

POLYMERIZATION TECHNIQUES:

Normal polymerization & Interfacial polymerization Both are carried out in liquid phase.

Normal polymerization

It is carried out using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the process of polymerization.[39]

Interfacial polymerization;

It involves the reaction of various monomers at the interface between the two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase.

PHASE SEPARATION COACERVATION TECHNIQUE

The process variables are very important since the rate of achieving the coacervates determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable speed stirrer since as the process of microspheres formation begins the formed polymerizes globules start to stick and form the agglomerates. [23-28]

SPARY DRYING AND SPARY CONGEALING:

The polymer is firs dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. the drug in the solid form is then dispersed in the polymer solution under high speed homogenization.

SOLVENT EVAPORATION:

In this method, polymer is dissolved in organic solvent, and then the drug is either dissolved or dispersed in the polymer solution. Then the polymer-drug mixture is dispersed in liquid manufacturing vehicle phase with agitation to obtain appropriate sized microspheres. [29, 30]

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEM [31-36]

1. Microspheres in vaccine delivery

The prerequisite of a vaccine is protection against the micro organism or its toxic product. An ideal vaccine must fulfill the required of efficacy, safety, convenience in application and cost. Biodegradable delivery systems for vaccines that are given by parenteral rout may overcome the shortcoming of the conventional vaccine. Microspheres as a carrier offer specific advances including:

- Improved antigenicity by adjuvant action
- Modulation of antigen release
- Stabilization of antigen

2. Targeting using microparticulate carriers

The concept of targeting i.e. site specific drug delivery is a well established dogma, which is gaining full attention. Placement of the particles indiscrete anatomical compartment leads their retention either because of the physical properties of the environment of biophysical interaction of the particles with the cellular content of the target tissue.

3. Monoclonal antibodies mediated microspheres targeting

Monoclonal antibodies targeting microspheres are immunomicrospheres. This targeting is a method used to achieve selective targeting to the specific sites. Monoclonal antibodies are extremely specific molecules. This extreme specificity of monoclonal antibodies (Mabs) can be utilized to target microspheres loaded bioactive molecules to selected sites.

The MABs can be attached to microspheres by any o f the following methods

- Non specific adsorption
- Specific adsorption
- Direct coupling
- Coupling via reagents

4. Chemoembolisation

Chemoembilisation is an endovascular therapy, which involves the selective arterial embilisation of a tumour together with simultaneous or subsequent local delivery the chemotherapeutic agent the theoretical advantage is that such embolisations will not only provide vascularocclusion but will bring about sustained therapeutic levels of chemotherapeutics in the areas of the tumour.

5.Imaging

The microspheres have been extensively studied and used for the targeting purposes. Various cells, cell lines, tissues and organs can be imaged using radio labeled microspheres. The particle size range of microspheres is an important factor in determining the imaging of particular sites.

6. Topical porous microspheres

Microsphonges are porous microsphere having myriad of interconnected voids of particle size range 5-300 µm. these microsponges having capacity to entrap wide range of active ingredients such as emollients fragrances, essential oils, are used as the topical carries system

7. Surface modified microsphere

Different approaches have been utilized to change the surface properties of carriers to protect them against phagocytic clearance and to alter their body distribution patterns. The adsorption of the poloxamer on the surface of the polystyrene, polyester or poly methyl methacrylate microspheres renders them more hydrophilic and hence decreases their MPS uptake. Protein microspheres covalently modified by PEG derivatives show decreased immunogenicity and clearance. The most studied surface modifiers are:

- Antibodies and their fragments
- Proteins
- Mono-oligo- and polysaccharides
- Chelating compounds (EDTA, DTPA OR Desferroxamine)

EVALUATION OF FLOATING DRUG DELIVERY SYSTEMS

Various parameters that need to be evaluated in gastro retentive formulations which includes floating duration, dissolution profiles, specific gravity, content uniformity, hardness and friability in case of solid dosage forms.

Size and Shape Evaluation

The particle size and shape plays a major role in determining solubility rate of the drugs and thus potentially its bioavailability. The particle size of the formulation was determined using Sieve analysis, Air elutriation (BahcoTM) analysis, Photoanalysis, Optical counting method, microscope, Electroresistance counting methods (Coulter counter), Sedimentation techniques, Laser diffraction methods, ultrasound attenuation spectroscopy , Air Pollution Emissions Measurements etc.

Buoyancy Lag Time

Buoyancy lag time (BLT): The time taken for dosage form to emerge on surface of medium called floating lag time (FLT) or buoyancy lag time (BLT).

Buoyancy time: The time during which the dosage form remains buoyant were measured.

Floating Time

Test for buoyancy is usually performed in (SGF) Simulated Gastric Fluid maintained at 370°C.The time for which the dosage form continuously floats on the dissolution media is termed as floating time.

Specific Gravity *I* Density

Density can be determined by the displacement method by using benzeneas displacement medium. The density of the system should be less than unity to confer the buoyancy of the system.

Water Uptake

It is an indirect measurement of swelling property of swellable matrix. In this the weighed dosage form is placed in the dissolution medium and removed out after a regular time interval and weight. The changes are determined with respect to time and swelling index is calculated by using the formula.

Swelling index= Changes in weight *I* Initial weight.

***In-Vitro* Release Studies**

In vitro dissolution test is generally done by using USP paddle type apparatus. The dosage form is placed on the dissolution medium. But sometimes as the vessel is large and paddles are at bottom, there is much lesser paddle force acts on floating dosage form which generally floats on surface. As floating dosage form not rotates may not give proper result and also not reproducible results. [37-41]

CONCLUSION

The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting, the goal in designing sustained or controlled delivery system is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action reducing the dose required, or providing uniform drug delivery.

BIBLIOGRAPHY

1. Anupama Sarawade, M.P. Ratnaparkhi, Shilpa Chaudhari, “Floating Drug Delivery System: An Overview”, Int J Res Dev Pharm L Sci. 2014, Vol.3(5), pp 1106-1115.
2. Stephen D. Bruck, Controlled drug delivery – Clinical applications, Vol 22, CRC press, inc., Florida(2000), pg :1 – 15.
3. Gwen M. Janseen and Joseph R. Robinson sustained and controlled dru delivery systems. In: Modern pharmaceutics, Gilbert. S. Banker and Christopher. T.Rhodes (eds), 14th Edition.
4. Remington; The science and practice of pharmacy, 20th Edition, Vol 1, Lippinkott Wilkins and Wilkins, Maryland, USP (2000), pg 903-930.
5. S.P. Vyas and R.K. Khur., Eds, Targeted and controlled drug delivery, first edition, CBS publishers, New Delhi, 2002, pg :331-386.
6. Krishnan. S. Targeted drug delivery systems, part-2. Drug lines, Vol-1, NO.2(1997) Aug, pg: 5-7.
7. Goodman & Gilman’s „The Pharmaceutical basis of therapeutics‟ eleventh edition (2005), edited by Laurance L. Broton, John. S. Lazo, Keith L. Parker, pg 673-679.
8. Alagusundaram. M., Madhusudanachetty, “Microsphrese as a noverl drug delivery system-Review”, International journal of pharmaceutics 2009, vol 1, issue 3, Pg 526-534.
9. The Indian Pharmacopeia. Vol-I, II, and III, the Controller of Publication, New Delhi, 2007.
10. Raymond C Rowe, Paul J Shesky and Marian E Quinn. Handbook of Pharmaceutical Excipients, 6thedn., Pharmaceutical Press and the American Pharmaceutical Association, London, 2009.

11. Mishra. A,R. Mazumder, M.sharma,"Formulation and evaluation of floating microsphere of amlodipine besylate by using ethylcellulose and HPMC"-Pharmacopore 2014, vol.5 (4), pg 602-609.
12. Swetha Kallepu, Madhavi Harika Srimathkandala, Vasudha Bakshi, "Formulation and evaluation of gastro retentive floating microspheres of nimodipine", Asian Journal of Pharmaceutics, Oct – Dec 2016 (Suppl), 10 (4) pg 628-635
13. Joselin Joseph, Dr. Sr. Daisy,P.A, Boby Johns George, R. Praveenraj, Noby Thomas, Dr. Sr. Betty Carla, "formulation and evaluation of floating microspheres of pantoprazole sodium", IJPPR Nov 2015,vol.:4 (4): pg 136-147.
14. Megha Sharma, Seema Kohli, Agnimitra Dinda, "Floating microspheres of repaglinide: formulation, optimization, characterization and *in- vitro* evaluation", Int.J.ChemSci.12(4), 2014, pp 1259-1272.
15. Navneet Garud and Akanksha Garud, "preparation and *in-vitro* evaluation of metformin microspheres using non-aqueous solvent evaporation technique", Tropical j. Pharm. Res. 2012, 11,(4): pp 577-583
16. Ramesh Y, Balachandra P, Chinnaiah S,"formulation and evaluation of floating microspheres of norfloxacin", Res. J. Chem .Env. Sci., 2013,vol: 1 (4), pp18-28.
17. Vinod Kumar, Pawn Jalwal, Jyoti, Tanuj Hooda, "formulation and evaluation of floating microsphere of ranitidine hydrochloride", IJPPR,2014,vol- 5(2), pp 1008-1015.
18. Mulugeta Fentie, AntenehBelete and Tsige Gebre-Mariam, "formulation of sustained release floating microspheres of furosemide from ethylcellulose and hydroxypropyl methylcellulose polymer blends", J.Nanomed Nano tech nol 2015, 6(1), pp 1-5
19. Mazumder. R, M.Sharma and A. Mishra, "formulation and evaluation of floating microsphere of amlodipine besylate by using ethylcellulose and HPMC", Pharmacopore, 2014, vol 5(4),pp 602-609.
20. Surendranath Betala, M. Mohan Varma, K.Abbulu, "formulation and evaluation of sustained release microspheres of metoprolol", IRJP, 2017,8(11) pp 103-108.
21. Avinash Y Kaushik, Ajay K Tivwari, Ajay Gaur, "preparation of floating microspheres of valsartan*: in-vitro* characterization", IJRAP, 2015, 6(1) pp 124-130.
22. Surendranath Betala, M. Mohan Varma, K. Abbulu, "formulation & evaluation of sustained release microspheres of propranolol",WJPPS,2017, vol 6(11) pp 1497-1507.
23. Sharma Tejal, Rawal Gaurav, "formulation and evaluation of floating microspheres of ranitidine", Int J Pharm Sci Rev Res, vol 12(2), 2012, pp-153 –156.
24. Shaji Jessy, ShindeAmol, "formulation and optimization of floating pulsatile aceclofenac microspheres using response surface methodology",IRJP,3 (1), pp 166 –169.
25. Kamini Vasava, Rajesh KS, Lalit Lata Jha, "formulation and evaluation of floating microspheres of cephalexin", IJPSRR, vol.11 (2) 2011, pp.69-75
26. Kapil Kumar, AkRai, "development and evaluation of floating microspheres of curcumin", Trop J Pharm Res, vol.11(5),2012.
27. Swapnila V Shinde (Vanshiv), RohitPawar, Hemant P Joshi, "domperidone floating microsphere: formulation and *in-vitro* evaluation", Journal of Pharmacy Researchvol.5(4),2012,pp 2235 – 2238.
28. M.Najmuddin, Sachin Shelar, Asgar Ali, V. Patel, T. Khan,"formulation and *in-vitro* evaluation of floating microspheres of ketoprofen prepared by emulsion solvent diffusion method", International journal of applied Pharmaceutics, vol.2(1),2010,pp 13-17.
29. Shankraiah M, Nagesh C, Venkatesh J S, Santhosh Raj M, Jagadish Rabadia, Sindhu Patil, "intragastric floating drug delivery system of levofloxacin:formulation and evaluation", JPSR, vol.3(6), 2011, pp 1265 – 1268.
30. Yuveraj Sing Tanwar, Pushpendra Singh Naruka, Garima Rani Ojha,"development and evaluation of floating microspheres of verapamil hydrochloride",RBCFvol43(4), 2007, pp 529-534.

31. Garima Chawla, Piyush Gupta, Vishal Koradia and Arvind K Bansal. Gastroretention: A means to address regional variability in intestinal drug absorption. Pharmaceutical technology. 2003; 27(2):50-68.
32. Mathiowitz, Edith ed., Encyclopedia of controlled drug delivery, vol-I, New York Wiley; 1999; 9-11.
33. H G Shivkumar, D Vishakante, Gwdaand T and M Pramod Kumar. Floating controlled drug delivery systems for prolong gastric residence. Indian.J.Pharm.Educ. 2004; 38 (4): 172-179.
34. Rouge N, Buri P and Doelker E. Drug absorption sites in the gastrointestinal tract and dosage form for site-specific delivery. Int.J.Pharm. 1996; 136:117-139.
35. Fell J T, Whitehead L and Collet H. Prolonged gastric retention using floating dosage forms. Pharm Technol. 2000; 24(3): 82-90.
36. Mathura R S and Sangahavi N M, Novel drug delivery systems for captopril. Drug. Dev.Ind.Pharm. 1992; 18:1567-1574.
37. Baumgartners S, Kristal J, Vrecer F, Vodopivec P and Zorco B. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int.J.Pharm. 2000; 195(1-2): 125-135.
38. Despande A A, Rhodes C T, Shah N H and Malick A W. Conrolles release drug delivery systems for prolong gastric recidence: an overview. Drug.Dev.Ind.Pharm. 1996; 22(6): 531-539.
39. Menon A, Ritschel W A and Sakr A. Development and evaluation of a monolithic floating dosage form for furosamide. J Pharm Sci. 1994; 83: 239-245.
40. Jimenez Castellanos MR, Zia H and Rhodes CT. Design and testing in-vitro of a bioadhesive and floating drug delivery system for oral application. Int J Pharm. 1994; 105: 65-70.
41. Watanabe K. Preparation and evaluation of intragastric floating tablet having pH independent buoyancy and sustained release property. Arch.Pract.Pharm Yakuzaigaku. 1993; 53: 1-7.