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A COMPREHENSIVE REVIEW ON FLOATING DRUG DELIVERY SYSTEMS

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ABSTRACT: Rate controlled drug delivery systems were developed to overcome physiological adversities like short residence times and unpredictable gastric emptying times. Differences in gastric physiology such as gastric pH and motility exhibit both intra and inter subject variability demonstrating significant impact on gastric residence time and drug delivery behaviour. This triggered an increased interest towards formulation of novel delivery systems which retained in the stomach for prolonged and predictable period of time. Several approaches such as floating drug delivery systems (FDDS), swelling and expanding systems, bio adhesive systems, modified shape systems, high density systems or other delayed gastric emptying devices have been discovered till now. FDDS are of particular interest for drugs that are locally active and have narrow absorption window in stomach or upper small intestine, unstable in the intestinal or colonic environment, and exhibit low solubility at high pH values. This review article is in pursuit of giving detailed information on the pharmaceutical basis of their design, Basic GIT physiology, GI motility, classification, advantages, limitations, Approaches to gastric retention, factors affecting FDDS, Polymers, Methods used for preparation and application of FDDS.

KEYWORDS: Floating drug delivery systems, Gastric residence time, Swelling index, Buoyancy.

1. INTRODUCTION

Floating systems explains that the systems are having low density, having a greater property of buoyancy to float over the gastric fluids present in stomach and help in maintaining of longer action[1]. Davis first identified floating systems in 1968. They are low-density systems with enough buoyancy to float over the gastric contents and stay in the stomach for an extended period of time[2]. The drugs which are having short biological half-life, they can be sustained by floating drug delivery system and their efficacy can be increased and help in decreasing the dosing frequency. This aspect of feds is assisting in increasing patient compliance and improving pharmacological therapy1. Based on granules, powders, capsules, tablets, laminated films and hollow micro spheres, several buoyant systems have been developed[3]. Floating drug delivery systems are intended to prolong the duration of the dosage form in the gastrointestinal tract while also assisting in the enhancement of absorption. Drugs that are more soluble in acidic conditions have a specific absorption located in the upper section of the small intestine, are more suited to these mechanisms[4]. Floating multi-particulates are gastro-retentive drug free-flowing protein or synthetic polymer powders, preferably smaller than 200 micrometres in size. Floating multi-particulates are gastro-retentive drug delivery systems which are based on non-effervescent and effervescent approach. Gastroretentive systems will remain for several hours in the gastric region and thus significantly extend the drug's gastric residence time. In a high pH setting, sustained gastric retention increases bioavailability, decreases drug wastes and improves solubility for drugs that are less soluble delivery systems based on non-effervescent and effervescent approach. In a strict sense,

hollow microspheres are empty spherical particles without a core[5]. Sustained release dosage forms are those that provide medication over a long period of time. The term "controlled release" refers to the system's ability to have some therapeutic control[6]. It is helpful in maximizing effectiveness and compliance. Usually, normal gastric residence time ranges from 5 min to 2 hrs.[3] Floating dosage forms are quickly gaining popularity as a promising new dosage form[5]. Floating dosage forms may be made as tablets or capsules by using appropriate excipients and including gas-generating agents, which give the dosage form buoyancy in gastrointestinal fluids[7]. The drug is slowly released at the optimal rate from the system while it is floating on the gastric contents. The residual system in the stomach is emptied after the medication is released[8].

1.1.Basic Gastrointestinal Tract Physiology:[10] The stomach is anatomically divided into 3 regions: fundus, body, and antrum (pylorus).

Fundus: proximal part.

Body: acts as a reservoir for undigested material,

Pylorus: it is a site for mixing of contents and acts as a pump for gastric emptying by propelling actions.

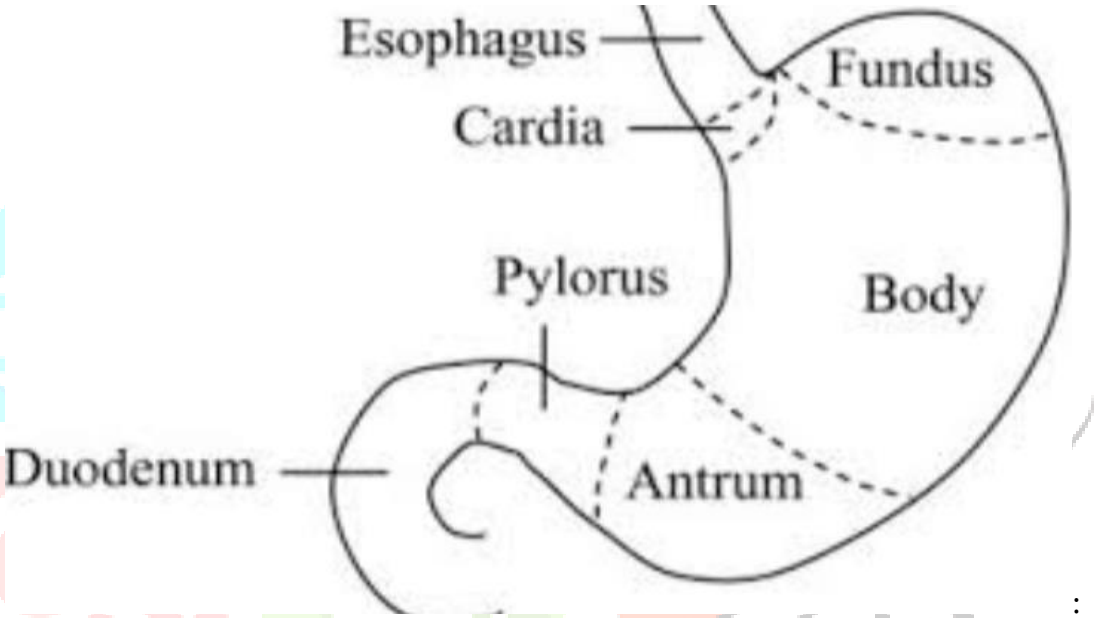

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Figure1: Stomach and its parts

1.2.Stomach Physiology: The stomach is an expanded digestive tube section present between the oesophagus and small intestine. The stomach is contracted in the empty state, the mucosa and sub mucosa are thrown up into distinct folds called rugae. Below are identified as the four major types of secretary epithelial cells which cover the surface of the stomach and extend into gastric pits and glands.

Mucous cells: secrete alkaline fluid.

Parietal cells: secretes an acid that is hydrochloric acid.

Chief cells: secrete pepsin, a proteolytic enzyme.

G cells: secrete the hormone gastrin

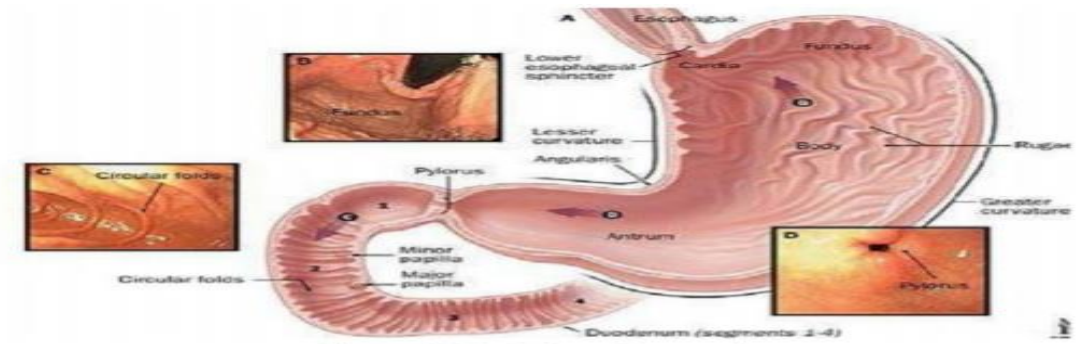


Figure 2: Physiology of stomach

1.3. Gastric motility: Gastric motility is being controlled by a complex set of neural and hormonal signals.

Gastric empty rate: Gastric emptying happens during both fasting and fed conditions. An inter-digestive sequence of electrical events take place during the fasting process, which pass every 2 to 3 hours in both the stomach and intestines. It is called the inter-digestive Mylo-electric cycle or myloelectric migratory cycle (MMC), which is further divided into 4 stages.

1. Phase I (Basal phase): It lasts from 40 to 60 minutes with rare contractions.

2. Phase II (Preburst phase): lasts for 40 to 60 minutes with intermittent action potential and contractions.

3. Phase III (burst phase): lasts for 4 to 6 minutes, which includes intense and regular contractions for short period of time.

4. Phase IV: lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.[10]

Figure 3: Motility Pattern in GIT.[9]

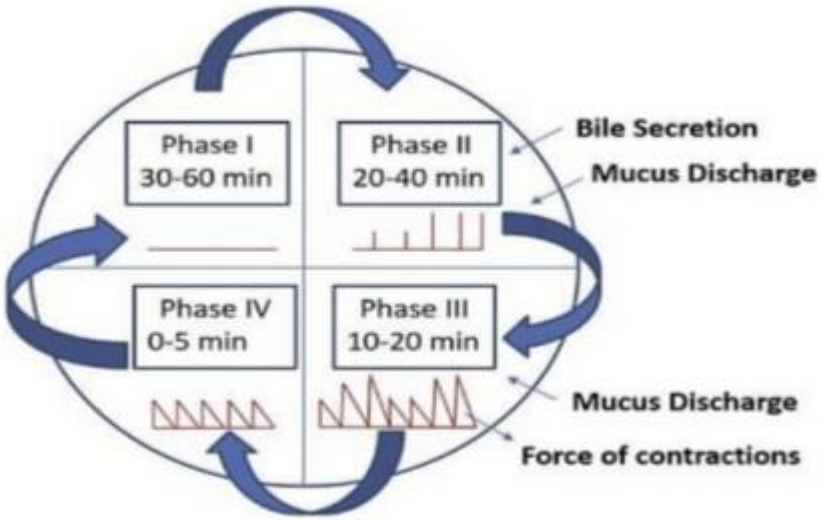


Figure 3: Motility Pattern in GIT.[9]

1.4. Advantages of floating drug delivery system. [25-29]

1. Increases the oral bioavailability of drug.

2. Enhanced first pass biotransformation.

3. Sustained drug delivery/ reduced frequency of dosing.

4. Reduced fluctuations of plasma drug concentration.

5. Improved receptor activation selectivity.

6. Provide higher efficiency due to reduced counter-activity of body.

7. Extended time over critical (Effective) concentration.

8. Minimized adverse activity at the colon.

9. Targeted therapy for local ailments within the upper GIT.

10. Site specific Drug Delivery.

1.5. Limitations of floating drug delivery system [30-34.]

1. Drugs having solubility or stability problem in GIT aren't suitable for FDDS.

2. Drugs like Nifedipine, Propranolol etc. which are well absorbed throughout GIT and which undergoes first pass metabolism are not desirable candidates.

3. Drugs which are irritant to Gastric mucosa also are not desirable.

4. Drugs that are unstable in the acidic environment of the stomach are not suitable in this type of systems.

5. High level of fluid in the stomach is required for maintaining buoyancy; float and work efficiently

2. Approaches to Gastroretention:

Several techniques are reported in the literature to increase the Gastroretention of drugs. [11-14]

Among many few major approaches are listed below.

2.1.High Density systems: These systems which have density of ≥3g/cm3, are retained in the rugae of stomach and capable of withstanding its peristaltic movements[11]. The only major drawback with these systems is that it is technically difficult to manufacture them with large amount of drug (>50%) and to achieve required density of 2.4-2.8g/cm3. Diluents such as barium sulphate, zinc oxide, titanium oxide and iron powder must be used to manufacture such high-density formulations.[15]

2.2.Swelling and Expanding systems: These systems are also as "Plug type systems", since they exhibit tendency to remain logged in the pyloric sphincters. These polymeric matrices remain in the gastric cavity for several hours even in the fed state.[16]

2.3.Mucoadhesive and bio adhesive systems: Mucoadhesive and bio adhesive systems are used to localize the deliver with device within the lumen to enhance the drug absorption in a site-specific manner. This approach involves the use of bio adhesive polymers, which can adhere to epithelial surface in the stomach. Some of most promising excipients that have been used commonly in these systems include polycarbophil, Carbopol, lectins, chitosan, CMC and gliadin etc.[17-18]

2.4.Low density systems: Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation.[26]

3. Classification of FDDS based on mechanism of bouncy:

3.1. Non effervescent systems: These are single-unit dosage forms, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC) is the most commonly used excipient; although ethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl agar, carrageen or alginic acid are also used. The polymer is mixed with drug and usually administered in a gelatine capsule. The capsule rapidly dissolves in the gastric fluid, hydration and swelling of the surface polymers produces floating mass.[19-20] Drug release is controlled by the formation of a hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layers, maintaining surface hydration and buoyancy.[21] Incorporation of fatty excipients gives low-density formulations and reduces penetration of water, reducing the erosion. Effective drug delivery depends on the balance of drug loading and the effect of polymer on its release profile.[22] Non effervescent system further classified into

1. Colloidal gel barrier system / Hydrodynamically balanced systems (HBS)

2. Micro balloons / Hollow microspheres.

3. Alginate beads.

4. Microporous compartment system.

5. Layered tablets.

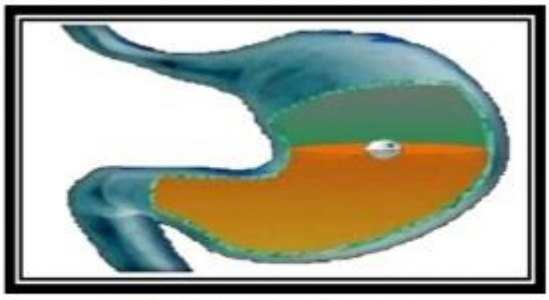
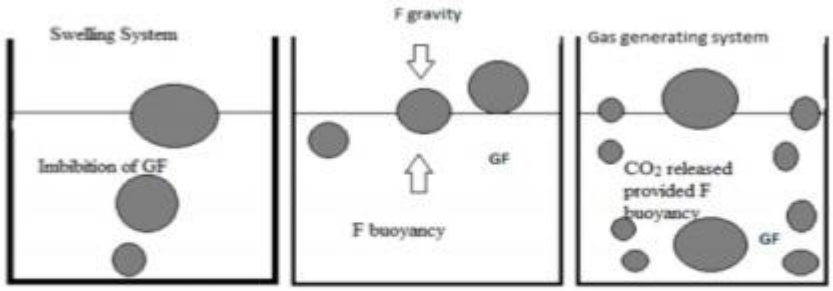


Fig: 3Floating Systems



Mechanism of floating system, GF = Gastric fluid

Fig: 4 The mechanism of floating systems

3.2. Effervescent systems: These are matrix type systems prepared with the help of swellable polymers such as Hydroxypropyl methylcellulose or polysaccharides and chitosan and various effervescent components like sodium bicarbonate, calcium carbonate, citric acid or tartaric. These dosage forms are developed in such a way that, when they come in contact with gastric juice in the stomach, Carbon dioxide is liberated and is trapped in the swollen hydrocolloids. This provides buoyancy to the dosage form. The liberated carbon dioxide may intimately get mixed within the tablet matrix in case of single layered tablet.[23]Effervescent system further classified into:

3.2.1. Gas generating system

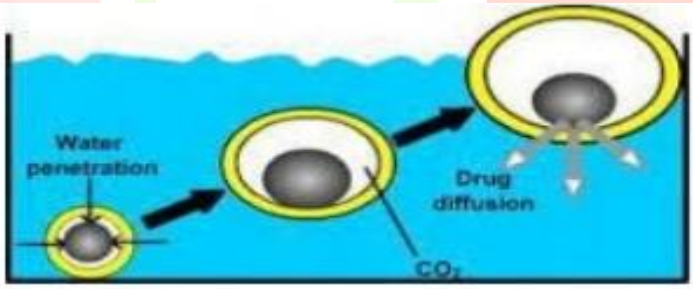


Fig:5 Principle Mechanism of floating by CO2gas releasing system

3.2.2. Volatile/Vacuum containing systems[24].

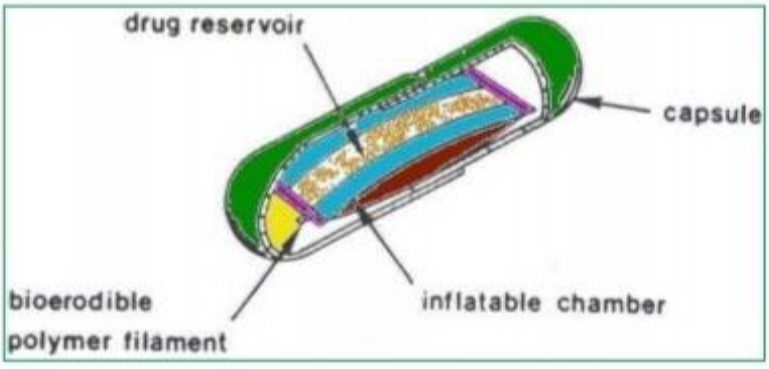


Fig: 6Volatile liquid containing systems

3.2.3. Raft Forming system: Here, a gel-forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles on contact with gastric fluid. Formulations also typically contain antiacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Because raft forming systems produce a layer on the top of gastric fluids, they are often used for gastroesophageal reflux treatment as with Liquid Gaviscon (GlaxoSmithKlGaviscon)

4.Factors controlling gastric retention of dosage forms. [9,10]

1. Density of dosage forms
2. Shape and size of the dosage form
3. Food intake and its nature
4. Shape of the dosage form
5. Fed or unfed state
6. Nature of meal
7. Frequency of feed
8. Gender
9. Age
10. Gastro intestinal pH
11. Concomitant administering of medications
12. Particle size
13. Emotional state
14. Exercise
15. Disease states

5. DRUG CANDIDATES SUITABLE FOR FDDS [26]

- Drugs having narrow absorption window in GIT (e.g., LDOPA, furosemide, P-aminobenzoic acid, riboflavin)
- Drugs which are locally active in the stomach (e.g., antacids, misoprostol)
- Drugs which are unstable in the intestinal environment (e.g., Metronidazole, ranitidine HCl, Captopril)
- Drugs having ability to affect normal colonic microbes (e.g., antibiotics used for the eradication of Helicobacter pylori, such as Clarithromycin, tetracycline, amoxicillin)
- Drugs having low solubility at high pH values (e.g., verapamil, diazepam, chlordiazepoxide).[28]

6. POLYMERS USED FOR FLOATING DRUG DELIVERY SYSTEM [11][25]

- Casein
- Cellulose acetate
- Chitosan and Sodium alginate
- Eudragit
- Polyvinyl alcohol
- Polycarbonate

7. Manufacturing methods of floating drug delivery system: The floating tablets are manufactured based on drug and excipients properties, duration intended for (immediate or sustained), stability of drug (against, temperature, oxidation, etc.,) and feasibility using below methods.[31]

1. Direct compression

2. Wet granulation

3. Dry granulation

8. Application of Floating Drug Delivery Systems: 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.[30]

9. CONCLUSION: As an important way to boost the bioavailability and controlled delivery of many medications, gastro-retentive floating drug delivery systems have emerged. The growing advanced delivery technology will optimize the delivery of molecules with a window of absorption, low bioavailability and extensive first pass metabolism. A potential approach to gastric retention promises to be a floating drug delivery method. While there are many obstacles to be tackled in order to achieve prolonged gastric retention, a significant number of businesses are focused on marketing this technique. It is a great challenge to devise an appropriate FDDS and research will continue until an optimal solution that can be applied on an industrial scale is found. The objective of floating drug delivery system (FDDS) is to improve the bioavailability of the drug with narrow absorption window in the gastric region. FDDS is helpful in reducing the frequency of dosing. However, there are many aspects which can be improved to achieve prolonged gastric retention.

10. References:

1. Aditya S, Vishkha C, Tahir N, Neelesh M, Namrata R, Vyas I. Formulation and Evaluation of Floating Tablet of Tropisetron Sharma. J Drug Deliv Ther. 2019; 9(2-A):44-6.

2. Pawar VK, Kansal S, Garg G, Awasthi R, Singodia D, K (1)1. Pawar VK, Kansal S, Garg G, Awasthi R, Singodia D, Kulkarni GT. Gastroretentive dosage forms: A review with special emphasis on floating drug delivery systems. Drug Deliv. 2011; 18(2):97- 110. https://doi.org/10.3109/10717544.2010.520354

3. Dey S, Singh PK. Bilayer and Floating-Bio adhesive Tablets: Innovative Approach to Gastroretension. J Drug Deliv Ther. 2011; 1(1):32-5. https://doi.org/10.22270/jddt.v1i1.26

4. Daisy Chella Kumari S, Vengatesh S, Elango K, Devi Damayanthi R, Deattu N, Christina P. Formulation and evaluation of floating tablets of Ondansetron Hydrochloride. Int J Drug Dev Res. 2012; 4(4):265-74. 5. Ojha A. Floating drug delivery system: A review. Journal of Drug DeliveryandTherapeutics.2014;4(2):130-4. https://doi.org/10.22270/jddt.v4i2.777

6. Gupta P, Gnanarajan PK, Kothiyal P. Floating drug delivery system: a review. International Journal of Pharma Research & Review. 2015; 4(8):37-44.

7. Sabale V, Sakarkar SN, Pund S, Sabale PM. Formulation and evaluation of floating dosage forms: An overview. Syst Rev Pharm. 2010; 1(1):33-9. https://doi.org/10.4103/0975- 8453.59510

8. Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: A Review. Research Journal of Pharmacy and Technology. 2008 Oct; 1(4):345-8.

9. Datir SK, Patil PB, Saudagar RB. Floating type drug delivery.

10. Dixit N. Floating Drug Delivery System. J Curr Pharm Res. 2011; 7(1): 6-20.

11. Chawla G, Gupta P, Koradia V, Bansal AK. Gastroretention: A Means to address regional variability in intestinal drug absorption. Pharm Tech 2003; 27: 250-268.

12. Muller-Lissner SA, Blum AL. The effect of specific gravity and eating on gastric emptying of slow-release capsules. New Engl JMed 1981; 304: 1365-1366.

13. Singh BN, Kim KH. Floating drug delivery system: An approach to the controlled drug delivery via gastric retention. J Control Release 2000; 63: 235-259.

14. Shah SH, Patel JK, Patel NV. Stomach specific floating drug delivery system: A review. Int J Pharm Res 2009; 1(3): 623-633.

15. Gergogiannis YS, Rekkas DM, Dallos PP, Chailis NH. Floating and swelling characteristics of various excipients used in controlled release technology. Drug Dev Ind Pharm 1993; 19: 1061-1081.

16. Bolton S and Desai S, 1989, US 4,814,179.

17. Patel R. Recent development in floating drug delivery system for gastric retention of drugs: anoverview.2007;http://www.swatijaini nst.com/etechno/feb2007/roma.rtf.

18. Asane GS. Mucoadhesive gastrointestinal drug delivery system: An overview. 2007; www.pharmainfo.net. ISSN: 2320-5407 Int. J. Adv. Res. 10(11), 161-167 166

19. Menon A, Ritschel W.A., Sakr A. Development and evaluation of a monolithic floating dosage form furosemide. J Pharm Sci. 1994; 83:239-245.

20. Oth M, Franz M, Timmermans J, Moes A. The bilayer floating capsule: a stomach directed drug delivery system for misoprostal. Pharm Res. 1992; 9:298-302.

21. Gohel M.C., Mehta P.R.., Dissolutiontech. 2004, 11(4), 22-25.

22. Karande A.D., Yeole P.G. Comparative Assessment of Different Dissolution Apparatus for Floating Drug Delivery Systems. Dissolutiontech.2006; 13(1):20-23.

23. Bhosale AR, Shinde JV, Chavan RS, A Comprehensive Review on Floating Drug Delivery System (FDDS), Journal of Drug Delivery and Therapeutics. 2020; 10(6):174-182.

24.Vedhahari b.n.et al, 2010. Development of a novel controlled-release system for gastric retention. Pharm Res.1997; 14:815-819.

25. Thakur N, Gupta BP, Patel D, Chaturvedi SK, Jain NP, Banweer J. A comprehensive review on floating oral drug delivery system. Drug Invention Today. 2 (7); 2010: 328-330.

26. Pooja gupta, Gnanarajan, Preethi K, Floating drug delivery system A review. Int J Phar Res Rev 2015;4(8):37- 44. 23. Dubey J, Verma N, Floating Drug Delivery System: A Review, IJPS

27. Dubey J, Verma N, Floating Drug Delivery System: A Review, IJPSR, 2013; 4(8):2893-2899.

28. Baviskar P, Patil P, Saudagar RB, Floating Drug Delivery System: A Comprehensive review, Journal of drug delivery and therapeutics, 2019; 9(3-s): 839-846.

29. Pakhale NV, Gondkar SB, Saudagar RB, Effervescent Floating Drug Delivery System: A Review, Journal of Drug Delivery and Therapeutics. 2019; 9(3-s):836-838.

30. Singh LP et al, Floating effervescent Tablet: A Review, JPBMS, 2011; 5(11):1-6. 11).

31. Pawar VK, Shaswat K, Garg G, Awasthi R, Singodia D, Kulkarni GT, Gastroretentive Dosage For ms: A review with special emphasis on floating drug delivery systems, Drug Delivery, 2011; 18(2):97-110. 32. Padhan et al, Floating Oral In-situ Gel, A Comprehensive Approach of Gastroretentive Drug Delivery System: A Review, IJPSR, 2019; 10(9):4026-4039.

33. Chowdary KPR, Shankar KR, Teeda V, Floating Drug Delivery Systems: A Review of Recent Research, IRJPAS, 2014; 4(4):14-24.

34. Grover I, Marwah M, Devgan M, Floating Drug Delivery systems: A Novel Approach, Research J. Pharm. and Tech. 2015, 8(4); 490-495