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REVIEW ARTICLE

Floating Tablets for *Helicobacter Pylori* Induced Peptic Ulcer Therapy: A Research Review on Formulation Studies, *In Vitro* and *In Vivo* Evaluation

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ABSTRACT

The purpose of writing this review on floating drug delivery system (FDDS) is to compile the recent research literature with focus on the gastro retentive tablet dosage forms. FDDS are of particular interest to deliver 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. In this review, current and recent developments of Stomach Specific FDDS are discussed. The recent developments of FDDS such as physiological and formulation variables affecting gastric retention, approaches to design single-unit floating systems and their formulation aspects are covered in detail. This review also summarizes the in vitro techniques, in vivo studies to evaluate the performance and application of floating systems, and applications of these systems. The pharmacokinetic evaluation aspects, roentgen graphic and Scintigraphy techniques were also discussed for evaluating efficacy of FDDS. The increasing technology of drug delivery will ensure the development of increase number of gastro retentive drug delivery to optimize the delivery of molecules that exhibit regional variability in drug absorption, low bioavailability and first pass metabolism. The research in this area is ongoing and it will not be long before improved systems could be developed.

KEYWORDS: Floating drug delivery system, Gastric residence time, Pharmacokinetics, Scintigraphy studies

INTRODUCTION:

Peptic ulcer (PU) is an open sore in the lining of the stomach or intestine usually caused by stomach acid and digestive enzyme pepsin. They are defects in gastric or duodenal mucosa extend through muscularis mucosa that may develop due to imbalance between acid amount and mucus defense which results in damage of lining in the stomach or duodenum by excess acid. PU is caused by *Helicobacter pylori* (*H.pylori*) bacteria, non steroidal anti inflammatory drugs, smoking and alcohol. The patients suffering from peptic ulcers with *h pylori* infection requires medication that addresses immediate symptomatic relief followed by rapid ulcer healing effect[1].

H. PYLORI BIOLOGY AND PU:

H. pylori live in the interface between surface of gastric epithelial cells and overlying mucus gel layer. In addition *h pylori* can also be found on top of the gastric epithelium in the duodenum and esophagus. *H. pylori* infection is the main cause associated with both gastric and duodenal ulcers. PU is due to an imbalance between aggressive and defensive mechanisms in stomach and duodenum. Part of that imbalance can be attributed to infection by *H. pylori*. Humans are the only known host of *h pylori*. Evidence of *H. pylori* infection in families, prisons, and nursing homes suggest that *h pylori* spread by close personal contact. However, exact mechanism for transmission is not well understood [2].

PU TYPES, SYMPTOMS AND CAUSES:

Depending upon their location, ulcers have different names. Gastric ulcer that occurs in stomach, duodenal ulcer develops in the first part of the small intestine and esophageal ulcer occurs in the lower section of esophagus. The PU patient shows symptoms like abdominal discomfort with gnawing ache, Sharp sudden persistent stomach pain and bloody or black stools. Other symptoms include weight loss, poor appetite, vomiting and occasional anorexia [3].

DIAGNOSTIC TESTS FOR *H. PYLORI*:

The ulcer causing *H. pylori* was diagnosed through blood, breath, stool, and tissue tests. Blood tests are most common to detect anti bodies to *H. pylori* bacteria. Histological evaluation, culture, polymerase chain reaction (PCR), and rapid urease tests are typically performed on tissue obtained at endoscopy. Alternatively, simple breath tests, serology, and stool assays are sometimes used, and trials investigating PCR amplification of saliva, feces, and dental plaque to detect the presence of *H. pylori* are ongoing [4].

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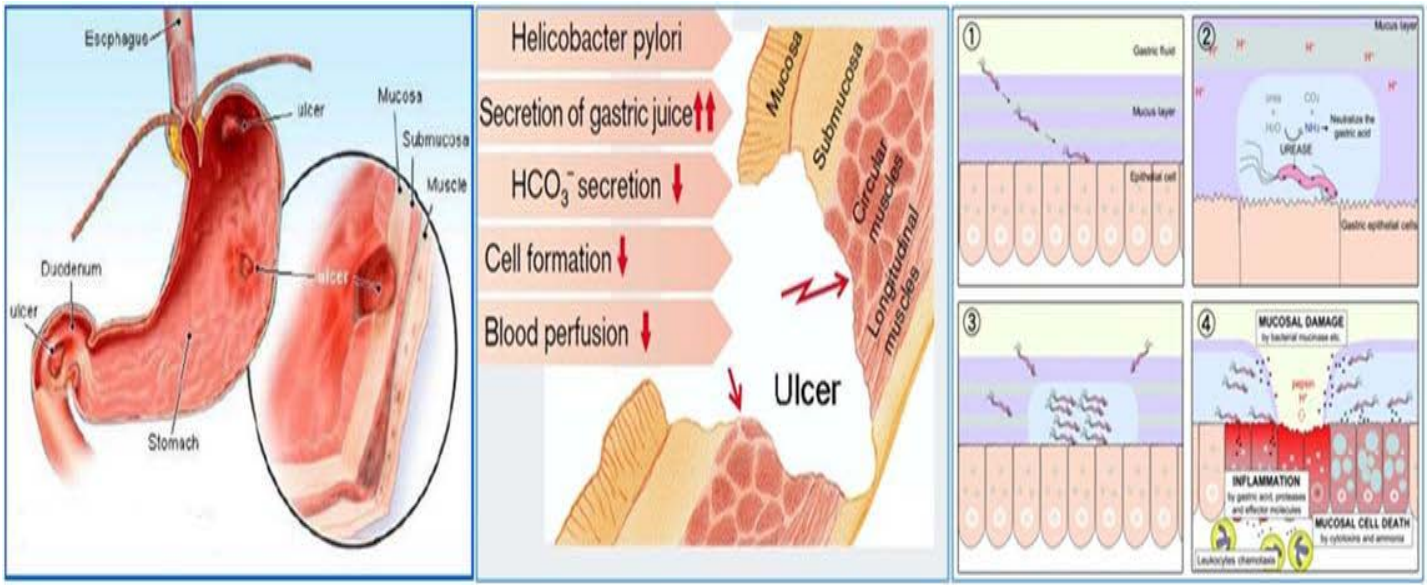

Figure No. 1. *H.Pylori* and hyper gastric acid secretion induced PUD causing mucosal damage

TREATMENT OF *H. PYLORI* CAUSED PU:

PU were treated mainly with acid suppressing drugs, like proton pump inhibitors suppress acid production by halting the mechanism that pumps the acid in to the stomach and H_2 receptor blockers work by blocking histamine [5]. Proton pump inhibitors: These are substituted benzimidazole compounds that specifically and irreversibly inhibit the proton pump hydrogen (potassium ATPase) in the parietal cell membrane. They are most powerful inhibitors of gastric secretion yet discovered, with maximal inhibition occurring 3-6 hrs after oral dose. They are esomeprazole, pantoprazole, rabeprazole, omeprazole and lansoprazole. Anti microbial and other agents: Clarithromycin, Amoxicillin, Metronidazole, Tetracycline and bismuth compounds acts as anti microbial agents against *h. pylori*. H_2 Blockers: Cimetidine, Ranitidine, Famotidine, Nizatidine acts as H_2 antagonists.

PROTON PUMP INHIBITORS APPROVED FOR *H. PYLORI* ERADICATION:

Esomeprazole (Nexium) 40 mg po per day; Lansoprazole (Prevacid) 30 mg po bid; Omeprazole (Prolisec) 20mg po bid; Pantoprazole (Protonix) 40 mg po bid; Rabeprazole (Aciphex) 20mg po bid.

U.S. FOOD AND DRUG ADMINISTRATION APPROVED DRUGS REGIMEN USED FOR PU THERAPY: [6]

a) Omeprazole (40 mg daily) plus clarithromycin (500 mg three times daily) for 2 weeks, then omeprazole (20 mg daily) for 2 weeks; b) Omeprazole (20 mg twice daily) plus clarithromycin (500 mg twice daily) plus amoxicillin (1 g twice daily) for 10 days; c) Lansoprazole (30 mg twice daily) plus clarithromycin (500 mg twice daily) plus amoxicillin (1 g twice daily) for 10 days; d) Lansoprazole (30 mg twice daily) plus amoxicillin (1 g twice daily) plus clarithromycin (500 mg three times daily) for 10 days; e) Esomeprazole (20 mg twice daily) plus clarithromycin (500 mg twice daily) for 2 weeks; f) Esomeprazole (40 mg daily) plus clarithromycin (500 mg twice daily) plus amoxicillin (1 g twice daily) for 10 days; g) Ranitidine bismuth citrate (400 mg twice daily) plus clarithromycin (500 mg thrice daily) for 2 weeks, ranitidine bismuth citrate (400 mg twice daily) for 2 weeks; h) Ranitidine bismuth citrate (400 mg twice daily) plus clarithromycin (500 mg twice daily) for 2 wk, ranitidine bismuth citrate (400 mg twice daily) for 2 weeks.

OVERVIEW OF GASTRO RETENTIVE DOSAGE FORMS (GRDF):

Dosage forms that can be retained in the stomach are called gastroretentive dosage forms (GRDF). GRDF can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability. Recent literature of research and patents has shown increased interest in novel dosage forms that can be retained in the stomach for a prolonged period of time that will provide important therapeutic options. GRDF are designed on the basis of one of the several approaches like formulating low density dosage form that remain buoyant above the gastric fluid or high density dosage form that is retained at the bottom of the stomach, imparting bio-adhesion to the stomach mucosa, expanding the dosage form by swelling

or unfolding to a large size which limits the emptying of the dosage form through the pyloric sphincter, utilizing ion exchange resin which adheres to mucosa, or using a modified shape system. Tablets have 2.7 ± 1.5 h stomach transit and 3.1 ± 0.4 h intestinal transit time [7].

FLOATING DRUG DELIVERY SYSTEMS (FDDS):

Floating systems, first described by Davis in 1968, 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 GRT and reduces fluctuation in plasma drug concentration. The advantages of FDDS includes; Gastric retention time is increased because of buoyancy, Site specific drug delivery to stomach can be achieved, Drug controlled release for a prolonged period and decreased dosing frequency, Targeted therapy for local ailments in the upper GIT, Better therapeutic effect of short half life drugs can be achieved, Enhanced absorption and first pass biotransformation of drugs soluble in stomach and reduced fluctuations of drug concentration could be achieved. But the FDDS are not feasible for drugs having solubility or stability problems in gastric fluid, High level of fluids in the stomach is required for maintaining buoyancy, Drugs with significant first-pass metabolism and drugs irritating gastric mucosa are not desirable candidates for FDDS. To formulate FDDS should dissolve slowly enough to serve as a drug reservoir with specific gravity lower than gastric contents (1.004–1.010), it must have sufficient structure to form a cohesive gel barrier and dissolve slowly to serve as drug reservoir [7].

EFFERVESCENT FDDS:

These buoyant systems utilize matrices prepared with swellable polymers like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid, or chambers containing a liquid that gasifies at body temperature. The common approach for preparing these systems involves matrix tablets loaded with bicarbonate and prepared with methocel K100 and methocel K15M by effervescent technique. When the dosage form is hydrated carbon dioxide is released and entrapped in the matrix causing it to float in the stomach.

NON EFFERVESCENT SYSTEMS:

These systems incorporate a high level (20-75% w/w) of one or more gel forming, highly swellable, cellulosic hydrocolloids, polysaccharides, or matrix-forming polymers into tablets. On contact with gastric fluid, they hydrate and form a colloidal gel barrier that controls the rate of fluid penetration into the device and consequent drug release. The air trapped by the swollen polymer lowers the density and confers buoyancy to the dosage form.

EVALUATION OF FDDS PROPERTIES:

In vivo characterization of FDDS Should be conducted and it may include evaluation of floating time, floating lag time, extent of expanding, effect of GRT on the mechanical integrity, dimension, and biodegradation, bioadhesive mechanism, mechanism of prolonged gastroretentive and evacuation. To characterize FDDS the following techniques recently introduced for pharmaceutical application, Gammascintigraphy involves identification of intragastric location of the dosage forms and dissolution, disintegration properties. A major advantage of this technique is its high safety profile as it is accompanied by relatively low dose of radiation. Radiology method is the state of art in preclinical evaluation of gastroretentive. Its major advantage as compaired to gammascintigraphy is simplicity and cost. Gastroscopy is preoral endoscopy used with fiberoptic or video system. Recently gastroscopy was used to evaluate the extent that unfolding FDDS. Magnetic marker monitoring technique developed by Weitschies et al., ensures very sensitive biomagnetic measurement equipment and magnetically marked dosage form. In ultrasonography method ultrasonographic waves reflected at substantially different acoustic impedance across an interface enable the imaging of some abdominal organ.

RESEARCH REVIEW STUDIES:

Gusler G et.al.[8] compared pharmacokinetics of gastroretentive metformin hydrochloride tablets in fed healthy volunteers with immediate release marketed product. The plasma concentration time profiles demonstrated extended release characteristics from the gastric retentive tablets. The mean bioavailability from each gastric retentive tablet was 115%. C_{max} values were lower and t_{max} values were greater for the gastric retentive tablets compared with marketed product. They concluded that the gastric retentive tablets showed extended release plasma concentration profiles of metformin hydrochloride and increased bioavailability compared with the immediate release tablet. Steingoetter A et.al., [9] determined the influence of meal composition and timing of tablet administration on the intragastric performance of a gastroretentive floating tablet using magnetic resonance imaging in the sitting position. The tablet showed persistent good intragastric floating performance

independent of meal composition. Mukesh C. Gohel et.al. [10] developed a more relevant *in vitro* dissolution method to evaluate a carbamazepine floating drug delivery system. A 100-ml glass beaker was modified by adding a side arm at the bottom of the beaker so that the beaker can hold 70 ml of 0.1 N HCl dissolution medium and allow collection of samples. A burette was mounted above the beaker to deliver the dissolution medium at a flow rate of 2 ml/min to mimic gastric acid secretion rate. The apparatus was compared with USP dissolution Apparatus 2 (Paddle). The drug release followed zero order kinetics in the proposed method. Similarity factor f_2 of 57 was observed at 10% difference level. The proposed test may show good *in vitro-in vivo* correlation to mimic the *in vivo* conditions. Krishnaiah YSR [11] developed and evaluated guar gum matrix tablets of rofecoxib by wet granulation technique and was subjected to *in vitro* drug release studies. The guar gum matrix tablet RXL-70 was evaluated *in vivo* in human volunteers to find their colon targeting ability of rofecoxib. They concluded that the delayed T_{max}, prolonged absorption time (t_a), decreased C_{max} and decreased k_a indicated that rofecoxib was delivered to colon resulting in a slow absorption of the drug and making it available for local action in human colon. Hossein Amini and Abolhassan Ahmadiani [12] developed a HPLC method for the determination of clarithromycin in human plasma with norverapamil as internal standard using a CN column with Acetonitrile:Sodium dihydrogen phosphate (32:68 v/v), pH 4.5. Detection was made at 205 nm and analyses were run at a flow-rate of 1.0 ml/min at 40^0C. The analysis time was less than 11 min. The method was specific and sensitive with a quantification limit of 31.25 ng/ml and detection limit 10 ng/ml in plasma. The mean recovery of clarithromycin from plasma was 95.9%, while the intra and inter day coefficient of variation and percent error values of the assay method were all less than 9.5%. Linearity was assessed in the range of 31.25–2000 ng/ml in plasma with a correlation coefficient of greater than 0.999.

Armagan Onal and Aysel Oztunc [13] developed and validated HPLC method for the analysis of esomeprazole magnesium trihydrate (ES) in tablets using C_{18} column with a mobile phase of acetonitrile/phosphate buffer (60:40, v/v, pH 7) at a flow rate of 1.0 ml/min with UV detection at 205 nm. Lansoprazole was used as an internal standard (IS). The calibration curve of ES was linear in the range of 100-1000 ng/ml (r = 0.9992, n=4). The RSD values for intra and inter day precision were 0.66-0.86% and 0.84-1.11%, respectively. The proposed method was successfully applied to the determination of ES in tablets. The mean recovery was between 97.82-98.22%. They concluded that above method can be used for routine quality control analysis. Atul D. Karande and Pramod G.Yeole [14] studied the effect of modifications in dissolution conditions on the floating drug delivery system by placing them in the dissolution apparatus, in accordance with the USP type 2 (paddle) method, placing them in a helical wire sinker (USP recommended) below the designed mesh device for achieving full surface exposure to the dissolution medium, and subjecting them to the dissolution in a modified dissolution apparatus. Results indicate that the overall release profiles from floating drug delivery systems of cefuroxime axetil are sensitive to their positioning in the dissolution apparatus. They concluded that the modified method provided reproducible dissolution profile and *in vivo* simulation. Ravala JA. et.al. [15] designed Ranitidine floating matrix tablets by the direct compression technique, consisting of a poly (styrene-divinyl benzene) copolymer low density powder. The effect of the addition of low density copolymer and the drug release pattern were also studied. The release rate was modified by varying the type of matrix forming polymer, the tablet radius and addition of water soluble or insoluble diluents. The highly porous copolymer provided a low density and, thus, excellent *in vitro* floating behavior of the tablets at a concentration of 15% (w/w). Jaimini M., Rana A.C and Tanwar Y.S. [16] prepared famotidine floating tablets with methocel K100, methocel K15M and Sodium bicarbonate and were evaluated. The tablets exhibited good physico chemical characteristics. All batches showed good *in vitro* buoyancy for 6-10 h. Decrease in citric acid increased floating lag time but tablets floated for longer duration. The tablets with methocel K100 floated for longer duration than methocel K15M tablets. The drug release from tablets was sustained with non fickian transport. Patel B.H et.al.,[17] developed and validated high performance liquid chromatographic method for the analysis of pantoprazole, rabeprazole, esomeprazole, domperidone and itopride, with ultraviolet detection at 210 nm. The compounds were well separated on a Hypersil BDS C18 reversed-phase column by use of a mobile phase consisting of 0.05 M, 4.70 pH, potassium dihydrogen phosphate buffer- acetonitrile (720:280 v/v) at a flow rate of 1.0 mL min^{-1}.The linearity ranges were 400-4,000 ng mL^{-1} for pantoprazole 200-2,000 ng mL^{-1} for rabeprazole 400-4,000 ng mL^{-1} for esomeprazole 300-3,000 ng mL^{-1} for domperidone and 500-5,000 ng mL^{-1} for itopride. Limits of detection (LOD) obtained were: pantoprazole 147.51 ng mL^{-1}, rabeprazole 65.65 ng mL^{-1}, esomeprazole 131.27 ng mL^{-1}, domperidone 98.33 ng $mL^{-1}$and itopride 162.35 ng mL^{-1}. The method used was sensitive and selective for the determination of pantoprazole, rabeprazole, esomeprazole, domperidone and itopride using single mobile phase.

Patel D.M et.al., [18] prepared floating tablets of carbamazepine using melt granulation technique. A simplex lattice design was applied to investigate the combined effect of 3 formulation variables i.e. amount of hydroxypropyl methylcellulose (X_1), ethyl cellulose (X_2) and sodium bicarbonate (X_3). The floating lag time (F_{lag}), time required for 50% (t_{50}) and 80% drug dissolution (t_{80}) were taken as responses. Results of multiple regression analysis indicated that, low level of X_1 and X_2, and high level of X_3 should be used to get the tablet with desired *in vitro* floating time and dissolution. Formulations developed were fitted to various kinetic models for drug release. Formulation S3 was selected as a promising formulation and was found stable at 40 ^{o} C and 75% relative humidity for 3 months. Muralidhar Nama et.al., [19] developed Clarithromycin hydrodynamically balanced tablet by wet granulation for the treatment of *H. pylori* mediated peptic ulcer. The proportion of sodium bicarbonate was varied to get the least possible lag time, also the polymer part varied to get the desired release. The formulation developed using 66.2% Clarithromycin, 12% HPMC K4M polymer, 8% sodium bicarbonate gave floating lag time less than 3 min with a floating time of 12 h, and an *in vitro* release profile very near to the desired release anomalous diffusion transport and follows zero order kinetics. *In vivo* radiographic studies suggest that the tablet has increased gastric residence time of 220±30 min for the effective localized action of drug in the treatment of *H. pylori* mediated peptic ulcer. Meka Lingam et.al. [20] designed and evaluated a biphasic gastroretentive floating drug delivery system with multiple-unit mini-tablets based on gas formation. The formulations were evaluated for quality control tests, and all the parameters evaluated were within the acceptable limits. The rapid floating and the controlled release properties were achieved in this present study. The similarity factor of formulation with coating of RS: RL (1:3)– 7.5%, was observed to be 74, which is well fitted into zero-order kinetics. The stability samples showed no significant change in dissolution profiles ($p>0.05$). *In vivo* gastric residence time by radiograms showed retention in stomach for about 5 h. Ashish Jain et.al. [21] prepared and evaluated a ranitidine hydrochloride floating delivery system with calcium silicate (CS) as a porous carrier, HPMC K4M and ethylcellulose (EC) as matrix-forming polymers. The formulation showed favorable *in vitro* floating and sustained drug release characteristics. The *in vivo* evaluation of pharmacokinetic parameters in albino rats showed higher plasma concentrations. The results suggested that CS is a useful carrier for the development of floating and sustained release preparations. Pablo Emilio et.al. [22] studied metronidazole floating systems with sodium bicarbonate (SB), Methocel K4M and Carbopol 971P NF. Pure Carbopol matrices show a rapid hydration with a limited further effect of the SB and metronidazole loads. Methocel show a significant increase of the apparent hydration volume due to SB addition. Methocel matrices released the drug 10% to 15% faster than Carbopol matrices. SB increases the cumulative amount of drug released from Methocel but not that releasing from Carbopol. These results are attributed to the intrinsic polymer properties, the barrier effect of CO_2 bubbles, and the matrix volume expansion produced after addition of SB. Nafisur Rahman, Zehra Bano and Syed Najmul Hejaz Azmi [23] developed two spectrophotometric methods for the determination of esomeprazole magnesium in commercial dosage forms. Method A is based on the reaction of esomeprazole magnesium with 5-sulfosalicylic acid in methanol and formed a yellow product, which absorbs maximally at 365 nm. Method B utilizes the reaction with N-bromosuccinimide in acetone-chloroform to form α-bromo derivative peaking at 380 nm. Beer's law is obeyed in the ranges of 2-48 and 10-100 μgmL^{-1} with molar absorptivity of $2.11x10^4$ and $4.57\ x10^4$ $Lmol^{-1}\ cm^{-1}$ for methods A and B, respectively. The limits of detection for methods A and B are 0.35 and 0.46 μgmL^{-1}, respectively with good accuracy and precision. Inez Jimenez Martinez et.al., [24] studied *in vitro* release of captopril from floating tablets, by varying Metolose and bicarbonate levels. Results indicated that matrices compacted at 55 MPa floated for > 8 h while those compacted at 165 MPa float only when sodium bicarbonate is included in the formulation. The matrices hydration volume increases with inclusion of sodium bicarbonate. The matrix density was lower when compacted at 55MPa. The drug release constant (k) decreased and the exponent (n) increased with increasing polymer contents. The drug released in less time when sodium bicarbonate is included in the formulation. Thakkar VT. et.al. [25] developed floating levofloxacin tablets by the direct compression method using Gelucire and HPMC as matrix formers and studied kinetics of drug release by applying mathematical and model dependent approaches. The *in vitro* drug release was studied in pH 1.2 HCl using USP dissolution Apparatus 2. Drug release from the optimal batch followed Higuchi model. The difference in percent deviation of area under the curve at each point was lowest for the optimum batch. They found that drug release was a function of the ratio of hydrophobic to hydrophilic matrixing agent. Monica RP Rao. et.al., [26] formulated and optimized salbutamol sulfate effervescent floating tablet by wet granulation. A 3^2 full factorial design (eight runs) was utilized to optimize the formulation wherein the content of hydroxypropyl methyl cellulose

(HPMC) (X_1) and sodium bicarbonate (X_2) were taken as independent variables and % drug release after 6 h (Y_1), $t_{50\%}$ (Y_2), and buoyancy lag time (BLT) (Y_3) were taken as the dependent variables. The *in vitro* drug release mechanism showed anomalous transport. An increase in the concentration and viscosity of the polymer decreased release rate. Concentration of both HPMC and sodium bicarbonate had a significant effect on the BLT. A good correlation was observed between predicted and actual values of the dependent variables chosen for the study.

Belgamwar V.S and Surana S.J., [27] formulated effervescent gastro retentive tablets with floating, swellable and bioadhesive properties. *In vitro* drug release followed the Higuchi kinetics and the release mechanism was found to be non fickian type. Rajeev garg and Gupta G.D. [28] formulated Acyclovir floating effervescent tablets by HPMC K4M, K5M, psyllium husk, swelling agent as crospovidone and microcrystalline cellulose and gas generating agent like sodium bicarbonate and citric acid and evaluated for floating properties and *in vitro* drug release studies. Floating non effervescent tablets were prepared by polypropylene foam powder and different matrix forming polymers like HPMC K 4M, Carbopol 934P, xanthan gum and sodium alginate. *In vitro* drug release studies were performed and drug release kinetics evaluated using the linear regression method was found to follow both the Higuchi and the Korsmeyer and Peppas equation. The drug release mechanism was found fickian type in most of the formulations. Ajit Kulkarni and Manish Bhatia. [29] designed bilayer regioselective floating tablets of atenolol and lovastatin to give immediate release of lovastatin and sustained release of atenolol. Sodium bicarbonate was used as a gas generating agent. All formulations were floated for more than 12 h. More than 90% of lovastatin was released within 30 min. HPMC K100M and xanthan gum sustained retarded the release of atenolol from the controlled release layer for 12 h. Diffusion exponent (n) were determined for all the formulations (0.53-0.59). Atenolol followed a mixed pattern of drug release models. The optimized formulation was found to be buoyant for 8 h in stomach. Therefore, biphasic drug release pattern was successfully achieved through the formulation of floating bilayer tablets in this study. Arza RA, Gonugunta CS, Veerareddy PR. [30] developed ciprofloxacin Hcl floating tablets with hydroxypropyl methylcellulose, crospovidone, sodium starch glycolate, croscarmelose sodium and sodium bicarbonate. Formulations are evaluated for percentage swelling, *in vitro* drug release, floating lag time, total duration of floating, and mean residence time (MRT) in the stomach. The drug release of optimized formulation follows the Higuchi kinetic model, and the mechanism is found to be non-Fickian/anomalous according to Korsmeyer-Peppas (n value is 0.68). The similarity factor (f (2)) is found to be 26.17 for the optimized formulation, which the release is not similar to that of marketed produced (CIFRAN OD). *In vivo* radiographic pictures of the healthy volunteers showed 320±48.99 min MRT in the stomach. Amir Farshchi, et.al., [31] developed a sensitive liquid chromatographic method for the analysis of clarithromycin- a macrolide antibiotic- in human serum, using pre-column derivatization with 9-fluorenylmethyl chloroformate (FMOC-Cl).The method involved liquid–liquid extraction of the drug and an internal standard (amantadine) followed by pre-column derivatization of the analytes with FMOC-Cl. A mixture of 0.05 M phosphate buffer containing triethylamine (2 ml/l; pH 3.8) and methanol (17:83, v/v) was used as mobile phase and chromatographic separation was achieved on a Shimpack CLC-ODS column, fluorescence detector at 265 and 315 nm. The analytical method was linear over the concentration range of 0.025-10 µg/ml of clarithromycin in human serum with 0.025 µg/ml limit of quantification. The assay is sensitive enough to measure drug levels of human single dose studies.

RECENT ADVANCES IN STOMACH SPECIFIC FLOATING DOSAGE FORMS:

Ferdous Khan et.al., [32] formulated theophylline floating tablet by direct compression technique with Methocel K100M and Methocel K15MCR. Formulations were evaluated for *in vitro* buoyancy and drug release study was evaluated for 8 h. The release rate, extent and mechanisms were found to be governed by polymer and floating agent content. The content of active ingredient was also a vital factor in controlling drug release pattern. It was found that polymer content and amount of floating agent significantly affected the mean dissolution time, percentage drug release after 8 hours, release rate constant and diffusion exponent. Pallab Roy and Aliasgar Shahiwala [33] designed ranitidine hydrochloride floating tablet with time lagged coating using response surface methodology (RSM) for experiment, mathematical models and optimization study. The chosen independent variables, i.e. percentage weight ratios of ethyl cellulose to HPMC in the coating formulation and coating level (% weight gain) were optimized with a 3^2 full factorial design. Lag time prior to drug release and cumulative percentage drug release in 7 h were selected as responses. Results revealed that both, the coating composition and coating level, are significant factors affecting drug release profile. A second order polynomial equation fitted to the data was used to predict the responses in the optimal region. The optimized

formulation prepared according to computer-determined levels provided a release profile, which was close to the predicted values. Shan Lu et.al. [34] developed high-performance liquid chromatography tandem mass spectrometry (HPLC–MS/MS) to simultaneously determine enalapril and enalaprilat in human plasma with benazepril as internal standard. Analysis was performed on an Ultimate TM XB-C18 column with mobile phase consisting of methanol, water and formic acid (62:38:0.2, v/v/v). The linear calibration curves for enalapril and enalaprilat were both obtained in the concentration range of 0.638–255 ng/ml (r^2 ≥0.99) with the lower limit of quantification (LLOQ) 0.638 ng/ml. The intra-day precision was below 7.2% and inter-day was less than 14%, while accuracy was within ±8.7 and ±5.5%. They concluded that the developed method was fully validated and successfully applied to the pharmacokinetic study of enalapril maleate capsules in 20 healthy males. Rajeev Garg and Ghanshyam Das Gupta. [35] prepared and evaluated floating tablets of Silymarin with HPMC K 4M, K 15M, psyllium husk, crospovidone, microcrystalline cellulose and sodium bicarbonate with citric acid and evaluated for floating properties, swelling and *in vitro* drug release. Floating non effervescent tablets were prepared by polypropylene foam powder, HPMC K 4M, Carbopol 934P, xanthan gum and sodium alginate. *In vitro* drug release studies were performed and drug release kinetics evaluated using the linear regression method was found to follow both the Higuchi and the Korsemeyer and Peppas equation. The drug release mechanism was found fickian type in most of the formulations. Ramesh Bomma et.al., [36] developed floating matrix tablets of norfloxacin by wet granulation using HPMC K4M, HPMC K100M and xanthan gum to prolong gastric residence time. Tablets were evaluated for their physical characteristics, drug content, floating properties and *in vitro* drug release for 9 h. The tablets exhibited controlled and prolonged drug release profiles with non fickian diffusion of drug release, indicating water diffusion and polymer rearrangement played essential role in drug release. The *in vivo* radiographic studies revealed 180 ± 30 min gastric retention time of tablets in the stomach of fasting human volunteers.

PHARMACOKINETIC STUDIES AND DOSAGE FORM LOCATION TECHNIQUES IN G.I.T:

Quan Liu and Reza Fassihi [37] assessed the drug release kinetics of gastroretentive tablets in relation to the full or partial hydration and swelling of matrices under standard and modified United States Pharmacopeia (USP) apparatus II using symmetrical shape factor for theophylline, diltiazem hydrochloride and alfuzosin hydrochloride. Results indicated that the floating monolithic systems based on hypromellose and polyethylene oxide, both release profiles and swelling dynamics in accordance with the similarity factor (f_2) and symmetrical shape factor values were positively influenced with more predictable and reproducible drug release kinetics. The modified USP method provided for complete matrix hydration and swelling as the dosage form remained fully submerged, allowing for more reliable release mimicking the *in vivo* conditions. Prajapati S.T, Patel L.D and Patel D.M. [38] developed domperidone floating matrix tablets by wet granulation technique, using HPMC K4M, carbopol 934P and sodium alginate either alone or in combination. Tablets were evaluated for physical characteristics, *in vitro* release characteristics for 24 h. Floating matrix tablets based on combination of three polymers namely; HPMC K4M, carbopol 934P and sodium alginate exhibited desired floating and prolonged drug release for 24 h. Carbopol loading showed poor floating but helpful to control the release rate of drug. Libo Zhao et.al.[39] studied safety, tolerability and pharmacokinetics of phenoprolamine hydrochloride floating sustained tablets (PHFST) in healthy Chinese subjects. In single dose studies, no severe adverse events were observed in volunteers, and all adverse events were mild, AUC, C_{max} increased with dose at 30-120 mg, the absorption of drug was unaffected by food. The mean C_{max} of PHFST is proportional to dose, but not the AUC. Oral dosing regimen selected for subsequent Phase II/III clinical trials was 60mg of PHFST, b.i.d., and dose up to 120 mg, b.i.d. may be used to achieve better antihypertensive effect. Sauzet C et.al., [40] developed an innovative floating gastro retentive dosage form (GRDF), by inducing a low density dosage form containing high active pharmaceutical ingredient (API) using a hydrophobic dusty powder. The GRDF was characterized for apparent density, buoyancy, porosity and *in vitro* dissolution. They reported that, Incorporation of silicon dioxide allowed production of a floating sustained release dosage form with optimum floating properties, using classical wet granulation technique as new alternative to formulate sustain release dosage form. Noelia L. Gonzalez Vidal et.al. [41] evaluated influence of accelerated aging conditions on the drug content and *in vitro* dissolution stability of eleven different ciprofloxacin (CIP) 500 mg tablets. The determination was performed at time zero and after three (3M) and six months (6M) of storage, according to ICH accelerated aging conditions (40°C/75% RH). Although the storage conditions examined in the study affected the dissolution behavior of all CIP formulations, they did not have a significant effect on chemical stability. Samip S et.al. [42] developed domperidone gastroretentive tablet using

HPMC K4M, eudragit L100 and sodium bicarbonate by direct compression. The prepared tablets were evaluated for drug release, *in vitro* and *in vivo* studies. The *in vitro* drug release followed Higuchi model, with high correlation coefficient (r). The buoyancy studies revealed that the tablets remained in the stomach for 250±30 min in fasted rabbits.The stability studies indicated there was no significant change in buoyancy and drug content for 12 months. Ashik Ullah Md et.al. [43] conducted an open-label, randomized; 2-way crossover study was conducted in healthy Bangladeshi male subjects in compliance with the Declaration of Helsinki and International Conference on Harmonisation guidelines to assess the relative bioavailability and pharmacokinetic properties of test and reference formulations of esomeprazole 40 mg. They concluded from the study that the test and reference formulations met the FDA regulatory criteria for assuming bioequivalence and well tolerated in studied population of healthy volunteers with significant difference in T_{max}. Ray Neng Chena et.al., [44] prepared swellable and floatable GRDDS Losartan tablets combining hydroxyethyl cellulose (HEC), sodium carboxymethyl cellulose (NaCMC), and sodium bicarbonate at various compression pressures and were evaluated for swelling characteristics, floating capacity, *in vitro* and *in vivo* characterization. The tablets floated over SGF for more than 16 h and swelled to 2 cm in diameter within 3 h. The release patterns of Losartan from these tablets were pH-dependent. The mean bioavailability was approximately 164%, relative to the immediate release product (Cozaar). MRT and t_{max} values were greater and C_{max} values were lower for the GRDDS tablets compared with Cozaar. Suresh Bandari et.al., [45] developed a biphasic gastroretentive drug delivery system (GRDDS) of fenoverine. They concluded that the floating multiple matrix tablet containing HPMC showed zero-order release profile. Tadros M.I. [46] developed Ciprofloxacin hydrochloride gastroretentive controlled release drug delivery system with swelling, floating and adhesive properties. Swelling ability, floating behaviour, adhesion period and drug release studies were conducted in 0.1 N HCl at 37±0.5 ^{0}C. The tablets showed acceptable physicochemical properties. Drug release profiles followed non fickian diffusion. Statistical analysis of data revealed optimum formulations and better physical stability. Abdominal X-ray imaging of formula F10, loaded with barium sulfate, in six healthy volunteers revealed a mean gastric retention period of 5.50 ± 0.77 h.

Jin Guan. et.al., [47] formulated high density famotidine gastrio resident osmotic pump tablet. They found that the optimized formulation showed zero order release rate. Gamma scintigraphy in beagle dogs showed *in vivo* gastric residence time of 7 h. Sigal Saphiera et.al. [48] studied the gastrointestinal transit and gastric emptying of non disintegrating solid dosage forms in rats using X-ray imaging. Gelatin minicapsules were filled with barium sulfate, coated by Eudragit S100 and administered orally to rats followed by a solution of iodine based contrast agent iopromide. Gastric emptying of different sized capsules was studied. It was found that shortened capsules of 3.5 and 4.8mm length were emptied from the stomach whereas the commercial length 7.18mm capsules were retained. They found that X-ray imaging can be used for simple visualization and localization of solid dosage forms in rats in the fed state using shortened commercial minicapsules on rats. Amit Kumar Nayak and co workers [49] prepared hydrodynamically balanced systems of ofloxacin using lactose, HPMC K4M, PVP K 30 and liquid paraffin. All these formulations were floated well over 6 hrs with no floating lag time. They also showed sustained drug release over 6 h. Time for 50% release of ofloxacin was 2.47 ± 0.02 to 3.07 ±0.08 h. The *in vitro* drug release was dependent on HPMC K4M, PVP K 30 and liquid paraffin content. The drug release followed the higuchi model with anomalous transport mechanism. Shireesh Kiran R. et.al. [50] prepared famotidine gastro retentive tablets using HPMC K100LV, ethyl cellulose with sodium bicarbonate by wet granulation method. The prepared tablets exhibited satisfactory physicochemical characteristics. The tablet remained buoyant for 12 h. Final formulation released approximately 94.41% drug in 12 h *in vitro*, while the floating lag time was <75 sec. The optimized formulation was found to be buoyant for 12 h in stomach. The non fickian transport of the drug release from the tablets was observed. Gande S and Rao YM [51] prepared baclofen floating tablets by wet granulation technique. Kinetics of drug release from all tablets followed Higuchi kinetics indicated diffusion mechanism of drug release. Formulations with 20 mg and 40 mg drug showed similar release profiles. There was no significant change in the formulations during accelerated stability conditions for three months. X-ray imaging in six healthy human volunteers revealed a mean gastric retention period of 5.50±0.7 hrs for the selected formulation. They concluded from the above as a stable, sustained release effervescent floating matrix tablets of baclofen could be prepared by wet granulation technique.

Safaa S. El Gamal et.al. [52] developed floating matrix tablets of acyclovir with HPMC, Compritol 888 and sodium bicarbonate by direct compression. A 3^2 factorial design in design expert software (version 7.1.6) was applied to optimize the drug release profile systematically. The results of factorial design indicated that a high level of both HPMC (X_1) and Compritol 888 (X_2) favored the preparation of

floating controlled release of acyclovir tablets. The *in vitro* studies showed the release followed Higuchi diffusion kinetics. No significant change in drug release profiles and buoyancy of the floating tablets was observed during stability studies at 40°C/75% RH for 3 months. Liandong Hu et.al. [53] developed the dextromethorphan hydrobromide sustained release tablets using floating technique by orthogonal experiment design. The floating lag time of tablets is 3 min and duration of floating is 24 h. The data of physical parameters were all lie within the limits. Drug release at 12 h was more than 85%. The pharmacokinetic study showed slightly higher AUC of floating tablets than reference tablets with prolonged T_{max}. Ismail Salama [54] developed HPLC method for simultaneous determination of telmisartan (TELM) and hydrochlorothiazide (HCT) in human plasma using indapamide as internal standard using cyanopropyl column with methanol: ammonium acetate solution (35:65) as mobile phase at 1 ml/min flow rate at 270 nm. The method was validated over the concentration range of 1-10 µg ml^{-1} for TELM and 0.31-3.12 µg ml^{-1} for HCT in human plasma. Inter and intra run precision of TELM and HCT were less than 3.60% and the accuracy was less than 1.868%. They concluded that the developed method was sensitive and reproducible for the analyte estimation. Cuiping Chen et.al. [55] conducted a pharmacokinetic study of gabapentin delivered from a novel gastric-retentive dosage form versus an immediate release formulation, dose proportionality and effect of food on the pharmacokinetics of gabapentin was studied. They observed that the t_{max} was extended for gastroretentive gabapentin than immediate release formulation. A dose related increase in both the maximum plasma concentration (C_{max}) and the area under the plasma concentration time curve (AUC) was observed as the gabapentin dose increased from 600 to 2400 mg. Fed status and increased fat content delayed tmax and enhanced C_{max} and AUC in proportion to the fat content. The pharmacokinetics of gastroretentive gabapentin formulation indicated reduced dosing frequency with improved bioavailability. Praveen Nasa and Sheefali Mahant [56] designed metformin hydrochloride effervescent floating drug delivery system, using Methocel K100M and E50 by wet granulation method. The floating tablets were evaluated for pre compression properties as well as *in vitro* drug release. The prepared tablets exhibited good precompression characteristics and satisfactory *in vitro* release profiles with non fickian type transport mechanism. Gabriella Baki et.al. [57] developed floating zinc acetate dihydrate systems with metolose 90 SH and sodium bicarbonate. They found that due to the interaction of active and effervescent agent leading to an unpredicted increase in liquid take up amount. The disintegration time of tablets varied due to their interaction, they found that the buoyancy and dissolution of tablets were appropriate for a floating system. Panagiotis Barmpalexis et.al. [58] prepared and investigated nimodipine polyethylene glycol solid dispersions as effervescent controlled release floating tablets. They found that nimodipine exists as mod I microcrystals in the solid dispersions and is stable for at least a three month period. The tablets showed good floating properties and controlled release profiles, with drug release by swelling and erosion of the polymer matrix. Artificial neural networks were proved to be efficient tool in the optimization of the tablet formulations. Manish Ghimire et.al. [59] investigated *In vitro* erosion behavior of tablets using scintigraphic method by adsorbing radiolabel isotope on to activated charcoal. Tablet erosion was affected by the preparation method. The mean *in vivo* onset time for all tablets did not differ significantly among the three different erodible tablets, MG tablets showed highest correlation between *in vitro* and *in vivo* mean erosion profile. Doro zynskia et.al. [60] investigated l-dopa hydrodynamically balanced systems (HBS) where the differences in water ingress into the matrices were detected by non-invasive MRI. Matrices based on carrageenans subjected to rapid hydration and erosion, were not able to maintain satisfactory floating properties for a sufficiently l ong period of time. The application of carrageenans in mixtures with HMC promoted water uptake by HBS formulations. Dissolution data was fitted to Korsmeyer Peppas equation. Abolfazl et.al. [61] developed ciprofloxacin gastroretentive tablet by direct compression technique and evaluated. A very sensitive HPLC method was developed to measure drug in plasma. The floating lag time is < 20 s and duration of floating time is >24 h. The drug release mechanism followed zero order kinetics. Pharmacokinetic parameters indicated the developed GT formulation showed extended pharmacokinetic profile than conventional tablet.

Swati Punda et.al. [62] developed oral gastroretentive rifampicin by extrusion spheronization process, statistical experimental strategy was utilized to simultaneously optimize the amount of Carbopol and MCC. The *in vivo* gamma scintigraphy in human volunteers, demonstrated the dosage form was retained in the stomach for more than 320 min. The human data validates the design concept and signifies the potential of the developed system for stomach targeted delivery of rifampicin for improved bioavailability. Vinay Wamorkar et.al [63] fabricated and optimized metoclopramide hydrochloride gastro retentive drug delivery system with ethyl cellulose and sodium alginate. Sodium carbonate was incorporated

as gas generating agent. Their study showed that, tablet composition and mechanical strength influenced floating properties and drug release. A zero order drug release was observed for 24 hrs with high regression values. The difference in the release pattern and kinetics was due to the difference in swelling and erosion behaviors. Laurene wang smith et.al. [64] assessed single dose pharmacokinetics and relative bioavailability of naproxen and esomeprazole in a 4-way crossover study after administration of a fixed dose combination tablet of enteric-coated (EC) naproxen 500 mg and non-EC esomeprazole magnesium 20 mg (NAP/ ESO tablet). Forty healthy adults were randomized to receive 4 study treatments with a washout interval ≥12 days. Naproxen plasma profiles were similar between the NAP/ESO tablet and EC naproxen, although median t_{max} was longest for the NAP/ESO tablet (5.3 vs 3.5-4.0 hrs). The NAP/ESO tablet produced much shorter esomeprazole t_{max} than the EC esomeprazole formulation (0.45 vs 2.5 hrs). They concluded that there are no pharmacokinetic drug interactions between naproxen and esomeprazole. The NAP/ESO tablet is bioequivalent to EC naproxen, and as expected, the bioavailability of non EC esomeprazole from the NAP/ESO tablet is lower than the EC esomeprazole formulation. Pratima srivastava [65] carried out pharmacokinetics and excretion studies of an anti ulcer pharmacophore in *Sprague dawley* rats. They found that the compound was detectable in serum samples as early as 5 min post oral administration. The compound showed 2.1 h elimination half life. The C_{max} was 469.28 ± 45.52 ng/ml after 1 h. The absolute bioavailability of the CDRI 85/92 was 70.5% after oral administration. It was found to be excreted in urine (15% of the dose) in intravenously treated (bile duct cannulated as well as noncannulated) rats whereas, bile and feces depicted insignificant levels of the compound. They found that the pharmacophore compound exhibited anti ulcer activity with ideal pharmacokinetic profile.

FUTURE POTENTIAL FOR FDDS:

The control of drug release profiles through restraining the dosage form with the aid of gastroretentive technology has been a major aim of pharmaceutical research and development in the currently focussed area, the control of GI transit to regioselective delivery of drugs for better and enhanced pharmacokinetic profiles that might produce high blood serum drug levels with better bioavailability. This provides scope for development of new products with new therapeutic possibilities and substantial benefits for patients to reduce dose frequency and improved compliance for effective therapy.

Product	Technology	Active ingredient	Company
Zanocin OD	Effervescent floating system	Ofloxacin	Ranbaxy, India
Riomet OD	Effervescent floating system	Metformine HCL	Ranbaxy, India
Cifran OD	Effervescent floating Form	Ciprofloxacin	Ranbaxy, India
Inon Ace tabs	Foam based floating system	Simethicone	SatoPharm, Japan
Gabapentin GR	Polymer swelling: AcuForm	Gabapentin	Depomed, USA
proQuin XR	Polymer swelling: AcuForm	Ciprofloxacin	Depomed, USA
Glumetza	Polymer swelling: AcuForm	Metformin HCL	Depomed, USA
Metformin GR	Polymer swelling: AcuForm	Metformin HCL	Depomed, USA
Prazopress XL	Effervescent and swelling	Prazosin HCl	SunPharma, Japan
Metformin HCL LP	Minextab Floating	Metformin HCL	Galenix, France
Cafeclor LP	Minextab Floating	Cefaclor	Galenix, France
Tramadol LP	Minextab Floating	Tramadol	Galenix, France
Cipro XR	Erodible matrix system	Ciprofloxacin	Bayer, USA
Baclofen GRS	Floating & swelling	Baclofen	SunPharma, India
Coreg CR	Gastro retention	Carvedilol	Glaxosmithkline
Madopar	Floating, CR capsule	Levodopa	Roche, UK
Liquid gaviscon	Effervescent floating liquid	Alginic acid	R. B. Healthcare.
Valrelease	Floating capsule	Diazepam	Roche, UK
Cytotec	Bilayer floating capsule	Misoprostol	Pharmacia Ltd, UK
Topalkan	Floating liquid alginate	Aluminum magnesium	Perrie FabrieFrance,
Conviron	FDDS Colloidal gel	Ferrous sulfate	Ranbaxy, India

Table No. 1: Various marketed FDDS with active ingredients and delivery technologies [7]

CONCLUSIONS:

Floating dosage forms (FDDS) enable prolonged and continuous input of the drugs to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by a narrow absorption window [66-69]. Based on the literature surveyed, it may be concluded that floating drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. Hence, it can be concluded that these dosage forms serve the best to deliver anti secretory and antibiotic agents for the treatment of diseases like peptic ulcer related to the GIT and for facilitating regioselective delivery and prolonged action of drug in the dosage form.

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