IJPSR (2012), Vol. 3, Issue 06 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 09 February, 2012; received in revised form 16 March, 2012; accepted 14 May, 2012

STOMACH SPECIFIC DRUG DELIVERY SYSTEM AND ITS *IN VITRO-IN VIVO* EVALUATION: A REVIEW

Sudhir S. Waghmode*, Dhananjay R. Abhang, Manik B. Patil, Nitin A. Gangarde, Dinesh P. Patil and Sachin N. Ahire

K.B.H.S.S.Trust's Institute of Pharmacy, Bhaygaon road, Malegaon camp, Malegaon, Dist: Nasik– 423 105, Maharashtra, India

Keywords:
stomach specific,
gastric residence time,
buyonancy

Correspondence to Author:

Waghmode Sudhir Sonba

K.B.H.S.S.Trust's Institute of Pharmacy, Bhaygaon road, Malegaon camp, Malegaon, Dist: Nasik– 423 105, Maharashtra, India

ABSTRACT

Stomach specific drug delivery system has occupied importance due to requirement of drug for local action and for those drugs that remains unaffected due to action of gastric fluid. Oral rout is considered most natural, unpredicted, and safe due to its ease of administration, Patient acceptance and convenience. Oral controlled release delivery systems are programmed to deliver the drug in predictable time frame that will increase the efficacy and minimize the adverse effects and increase the bioavailability of drugs. In Stomach specific drug delivery system gastric retention can be achieved by forming bioadhesive system, swelling and expanding system, floating system and high density systems. In fact the buoyant dosage unit enhances gastric residence time (GRT) without affecting the intrinsic rate of emptying and gives prolonged effect of drug. Systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs and reduces dosing time. In this review various types of stomach specific dosage form and their in-vitro and in-vivo parameters for evaluation are discussed.

INTRODUCTION: It was suggested that compounding narrow absorption window drugs in a unique pharmaceutical dosage form with gastroretentive properties would enable an extended absorption phase of these drugs. As considering the need of the drug to have its local action on the stomach.

Stomach specific drug delivery systems are among the several approaches that have been developed in order to increase the gastric residence time of the dosage forms The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion, modified shape systems, or by the simultaneous administration of pharmacological agents that delay gastric emptying.

Both low and high-density drug delivery systems have been suggested as possible approaches to extend the transit time but the results of exploratory studies area equivocal [1]. In another system in which particle size, relative to stomach retropulsion has been suggested as a means to delay stomach emptying and thereby prolong transit time.

In case of floating drug delivery system the multiple unit system has been developed to identify the merit over a single unit dosage form because the single unit floating systems are more popular but have a disadvantage owing to their "all-or-nothing" emptying process, leading to high variability of the gastrointestinal transit time. The stomach specific drug systems are meant [2],

1. For the Drugs acting locally in the stomach;
2. For the Drugs that are primarily absorbed in the stomach;
3. For the Drugs that are poorly soluble at an alkaline pH;
4. Drugs absorbed rapidly from GI tract; &
5. Drugs that degrades in colon.

Gastric residence of the drug can be achieved by the decreasing the density lower than the gastric fluid. Fatty material with a bulk density lower than one may be added to the formulation to decrease the water intake rate and increase buoyancy. Floating systems includes matrices prepared from polymers that swells upon the absorption of gastric fluid and attains buyoncy.

An effervescent system includes the polysaccharides or Methocel and effervescent materials like citric acid, tartaric acid, sodium bicarbonate. Noneffervescent systems incorporate a high level (20–75 % w/w) of one or more gel forming, highly swellable, cellulosic hydrocolloids (e.g., hydroxyethyl cellulose, Hydroxy propyl cellulose, Hydroxy propyl methylcellulose (HPMC, and sodium carboxy methylcellulose, polysaccharides, or matrix-forming polymers (e.g., polycarbophil, polyacrylates, and polystyrene) into tablets or capsules [3].

An ideal dosage form is one, which attains the desired therapeutic concentration of drug in plasma and maintains constant for entire duration of treatment. This is possible through administration of a conventional dosage form in a particular dose and at particular frequency. In most cases, the dosing intervals much shorter than the half life of the drug resulting in a number of limitations associated with such a conventional dosage form are as follows:

Poor patient compliance; increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary. A typical peak plasma concentration time profile is obtained which makes attainment of steady state condition difficult. The unavoidable fluctuation in the drug concentration may lead to under medication or over medication as the steady state concentration values fall or rise beyond in the therapeutic range. The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index whenever overmedication occurs. The above problems can be overcome by the development of effective and safer use of existing drugs through concepts and technique of controlled and targeted drug delivery system. The controlled drug delivery system is one, which delivers the drug at a predetermined rate, locally or systemically for a predetermined period of time. The targeted drug delivery system is one, which delivers the drug only to its site of action and not to the nontarget organs or tissues [4].

The advantages of controlled drug delivery system over the conventional dosage forms are as follows**:**

- Improved patient convenience and compliance due to less frequent drug administration.
- Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Maximum utilization of drug and reduction in total amount of dose administered.
- Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing.

Despite the several advantages associated with oral controlled drug delivery systems, there are so many disadvantages, which are as follows:

- Basic assumption is drug should absorbed throughout GI tract.
- Limited gastric residence time which ranges from few minutes to 12 hours which lead to unpredictable bioavailability and time to achieve maximum plasma level Intersubject variability.
- Drug should not be targeted to specific region of GIT.

The above mention limitation of controlled release can be overcome by Gastro retentive system [5].

Types of stomach specific Drug Delivery System: Stomach specific drug delivery system includes the following type:

A. **Floating Drug Delivery System:** Drug delivery System with low density provides sufficient buoyancy to float over the gastric contents.[6] Fig.1.a.Gastric flotation can be achieved by formation of the dosage form filled with inert gas, or by incorporating vaccum or by formulating dosage form with the low density materials. FDDS floats on the chyme or gastric fluid due to its density lower than the gastric fluid. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system [7].

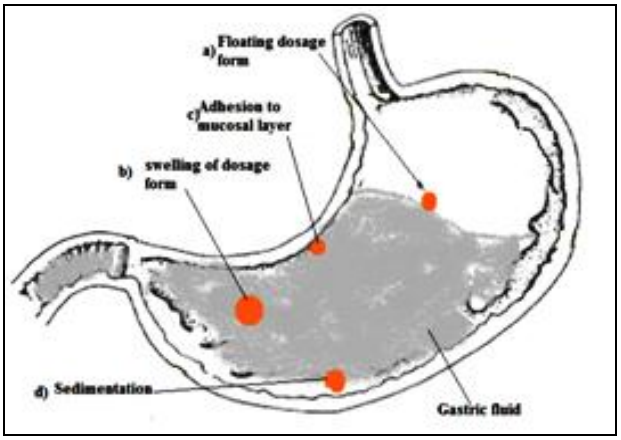


FIGURE 1: STOMACH SPECIFIC DRUG DELIVERY SYSTEMS

a. Floating gastro-retentive drug delivery systems; b. swelling gastro-retentive drug delivery systems; c. Bioadhesive gastroretentive drug delivery systems; d. High density gastro retentive drug delivery systems.

FDDS is further categorised as;

1. **Effervescent Systems:** This system involves the effervescence of CO_2 gas when the drug system comes in contact with the gastric fluid. It consist the effervescent substances like tartaric acid, citric acid, sodium bicarbonate which results in formation of gas and attains buyoncy [8].

a. **Volatile Liquid containing Systems:** In this Gastric retention is achieved by incorporating the volatile liquids like cyclopentane, ether in the inflatation chamber. Fig.2.These systems are osmotically controlled floating systems containing a hollow deformable unit. There are two chambers in the system first contains the drug and the second chamber contains the volatile liquid [9]. As at body temperature these volatile liquids converts into gas mean while dosage form system floats on the gastric fluid and releases drug at constant rate. The device may also consist of a bioerodible plug made up of PVA, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach [10].

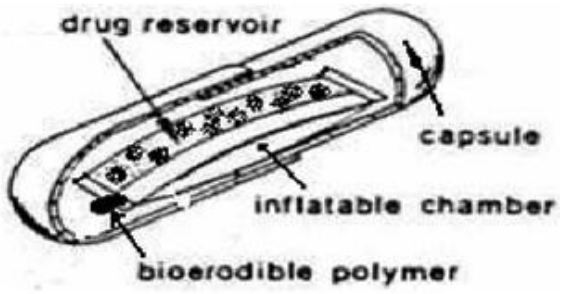
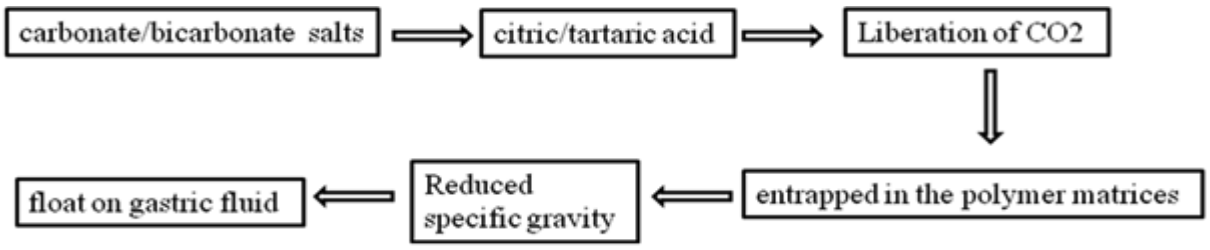


FIG. 2: INFLATATION CHAMBER

b. Gas Generating Systems: These buoyant delivery systems utilize effervescent reaction between carbonate/ bicarbonate salts and citric/tartaric acid to liberate CO2 which gets entrapped in the polymer matrices layer of the system, thus decreasing its specific gravity and making it to float on gastric fluid. And low density grade HPMC polymer allows ease of floating [11].



c. **Matrix Tablets:** It includes the gelling agents like alginate, HPMC and other polymers can be used with drug and sodium bicarbonate in matrix forming hydrocolloid gelling agent like HPMC, chitosan, alginate or other polymers and drug and on these formulation single or double layers are added for getting sustained release effect of drug. Cationic and anionic polymers bind more effectively to the mucosal layer [13].

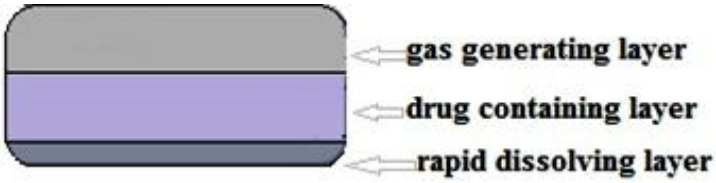


FIG 3: EFFERVESCENT MATRIX TABLET

2. **Non-effervescent systems:** Such formulations are formulated by using gel forming or swellable cellulose type of Hydrocolloids and other polymers having low specific gravity than 1.On entrapment of gas within swellable polymer matrix results in buyoncy. Incorporation of fatty excipients gives low-density formulations [13, 14].

a. **Hydrodynamically balanced systems:** In HBS polymers used are swellable hydrocolloids, Polysaccharides, polyacrylate, polymeth acrylate, and polystyrene like polymers and some other type of polymers having low specific gravity are also used.Fig1.b. The polymer is mixed with drug and usually administered in a gelatin capsule. The capsules rapidly dissolve in the gastric fluid, and hydration and swelling of the surface polymer produce a floating mass. This imparts buoyancy to dosage form in gastric juice for a long period [15].

Drug release is controlled by the formation of hydrated boundary at the surface. Continuous erosion of the surface allows water penetration to the inner layer, maintaining surface hydration and buoyancy. Incorporation of fatty excipients gives low density formulations and reduces penetration of water, reducing the erosion. But its limitation is the passivity of operation. It depends on the air sealed in the dry mass centre following hydration of gelatinous surface layer and hence the characteristics and amount of polymer. Effective drug delivery depends on the balance of drug loading and effect of polymer on its release profile.

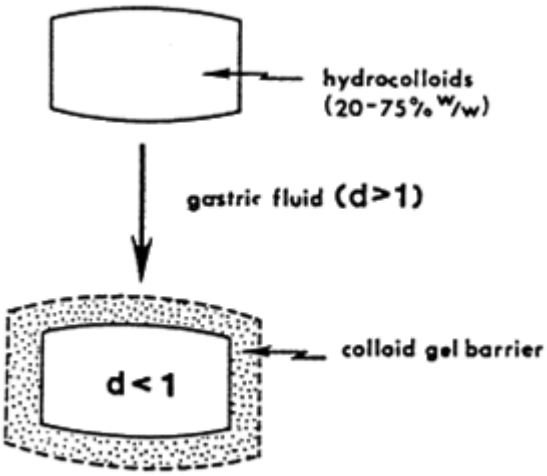


FIG. 4: INTRAGASRIC FLOATING TABLET

b. **Hollow microspheres:**

Preparation of Hollow Microspheres by Diffusion Method: Hollow microspheres are prepared by novel emulsion-solvent diffusion Method. The ethanol: dichloromethane solution of drug and enteric acrylic polymer was poured into an agitated aqueous solution of PVA that was thermally controlled at 400 C. The gas phase generated in dispersed polymer droplet by evaporation. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for more than 12 hours *in vitro*. Quantity of polymers and the plasticizer polymer ratio and also the solvent used for formulation determines buoyancy and drug release from dosage form.

Preparation of Hollow Microspheres by Evaporation Method: Hollow microspheres are prepared by evaporation methods to create the hollow inner core. Polymer is dissolved in an organic solvent and the drug is either dissolved or dispersed in the polymer solution. The solution containing the drug is then emulsified into an aqueous phase containing polyvinyl alcohol to form oil in water emulsion. After the formation of a stable emulsion, the organic solvent is evaporated either by increasing the

temperature under pressure or by continuous stirring. The solvent removal leads to polymer precipitation at the o/w interface of droplets, forming cavity and thus making them hollow to impart the floating properties.

c. **Alginate beads:** Alginate beads are prepared from the freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution into aqueous solutions of calcium chloride, causing precipitation of calcium alginate, separated and dried by air convection and freeze drying, leading to the formulation of a porous system. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at -40° for 24 h, which can maintain a floating force for over 12 hrs.

3. **Bioadhesive systems** : As in **fig. 1C** bioadhesive systems enable the localized retention of the system in the stomach. Floating-bioadhesive systems overcomes the drawbacks of floating and bioadhesive systems can have significant advantage and ultimately improve the therapeutic effect of the drug e.g., floating system are effective only when there is high fluid levels in the stomach, but bioadhesive polymers enable it to adhere to the mucous lining of the stomach wall [14] (**Fig. 5).** Mucoadhesive polymers used are carboxylic group containing hydrophilic polymer and hydrogels like poly vinyl pyrrolidone (PVP), Methyl cellulose (MC), Hydroxy propyl Cellulose (HPC) and other cellulose derivative are also used in stomach specific gastroretentive dosage forms.

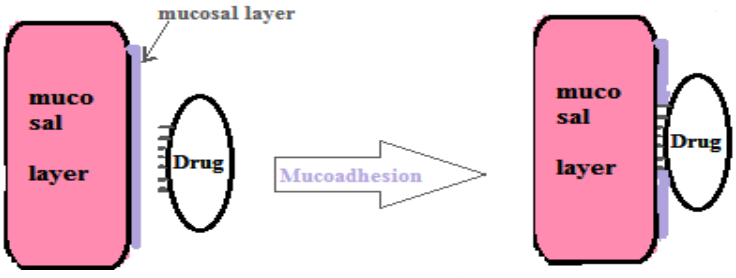


FIG. 5: MECHANISM OF MUCOADHESION

a. **Hydration-mediated adhesion** [15]: Certain hydrophilic polymers tend to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties.

b. **Bonding-mediated adhesion**: The adhesion of polymers to a mucus or epithelial cell Surface takes place by physical-mechanical bonding and chemical bonding. Physical-mechanical bonds are due to the insertion of the adhesive material into the crevices or folds of the mucosa. Chemical bonds may be either covalent (primary or ionic secondary) in nature. Secondary chemical bonds consist of dispersive interactions i.e., Vander Waals interactions and stronger specific interactions such as hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl and carboxylic groups.

c. **Receptor- mediated adhesion**: Certain polymers can bind to specific receptor sites on the surface of cells, thereby enhancing the gastric retention of dosage forms. Certain plant lectins such as tomato lectins interact specifically with the sugar groups present in mucus or on the glycocalyx [18].

Molecular characteristics: The molecular characteristics required for mucoadhesion are as follows.

A. Strong hydrogen-bonding groups -OH, -COOH

B. Strong anionic charges

C. Sufficient flexibility to penetrate the mucus network or tissue crevices

D. Surface tension characteristics suitable for wetting mucus/mucosal tissue surface

E. High molecular weight.

4. **Swelling and Expanding Systems:** These systems are sometimes referred to as plug type systems because they tend to remain lodged at the pyloric sphincter preventing transit from the gastric sphinctor. As shown in fig 1.b. [19], After swallowing dosage form it get retained in the stomach for a long period of time, these dosage forms swell to a size that prevents their passage through the pylorus. As a result, these polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled effect of drug depends on polymer property.

As dosage form gets imbibed due to contact with gastric fluid, and the polymer get swell which results into crosslink's in the hydrophilic polymer network .due to cross linking dissolution of polymer is prevented [20]. A high degree of cross linking retards the swelling ability of the system and maintains its physical integrity for a prolonged period. On the other hand, a low degree of cross-linking results in extensive swelling followed by the rapid dissolution of the polymer.

An optimum amount of cross-linking is required to maintain a balance between swelling and dissolution. The swollen system eventually will lose its integrity because of a loss of mechanical strength caused by abrasion or erosion or will burst into small fragments when the membrane ruptures because of continuous expansion. These systems also may erode in the presence of gastric juices so that after a predetermined time the device no longer can attain or retain the expanded configuration [21].

5. **High Density Systems:** Remaining in the stomach for longer period of time, by sedimenting to the folds of stomach. **Fig. 1d** illustrates the mechanism of these systems in stomach [20]. These systems with a density of about 3 g/cm^3 are formulated using diluents like barium sulphate, zinc oxide, titanium dioxide, iron powder. Due to its high density they are retained into antrum part of the stomach and are capable of withstanding its peristaltic movements. But these systems are difficult to manufacture by using high amount of drug (>50% and to achieve a density of about 2.8) [22].

6. **Raft Forming Systems:** Here, a gel forming solution (e.g., Sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO_2bubbles on contact with gastric fluid [22]. Formulations also typically contain antacids 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 the treatment of gastroesophageal reflux treatment.

7. **Magnetic Systems:** Dosage form contains small magnet internally remains buoyant in stomach due to magnetic attraction of magnet placed on the abdomen over the position of the stomach. This technique is used in rabbits with bioadhesive granules containing ultrafine ferrite (G-Fe2O3) [23.] They guided them to the oesophagus with an external magnet (1700 G) for the initial 2 min and almost all the granules were retained in the region after 2 h. Although these systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance [24.]

***In-Vitro* Evaluation parameters**

1) **Size and Shape Evaluation:** Particle size and the size distribution of the beads or microspheres are determined in the dry state by optical microscopy [25].

2) **Surface characterizations (for Floating Microspheres and Beads**): The external cross-sectional morphology is carried out by scanning electron microscopy SEM [25].

3) **Drug Loading Efficiency:** Accurately weighed sample of beads or microspheres crushed in a mortar and adding it to the appropriate dissolution medium this is then centrifuged, filtered and analyzed by a variety of analytical methods like Spectrophotometry [25].

$$\text{Percentage Drug Loading} = \frac{\text{Amount of Drug in Sample}}{\text{Weight of total Beads or Microspheres}}$$

4) **Buoyancy Lag Time:** It is time taken by the dosage form to float on the top of the dissolution medium, after it is placed in the medium. These parameters can be measured as a part of the dissolution test [28].

5) **Dissolution Studies:** In vitro dissolution test is generally done by using USP paddle type apparatus. Studies are usually carried out in SGF & SIF maintained at 37°C. It is done by placing tablet in a dry basket at the beginning of each test. Lower the Basket before rotation operates the apparatus immediately at 50 rpm Medium

used for release rate study was 900ml 0.1 N HCl during the course of study whole assembly was maintained at 37+0.5 ^{o}C. Withdraw a 5 ml of sample at specific time interval and replaced with 5 ml of fresh dissolution medium. The withdrawn samples were dilute with dissolution medium and then filter it with whattman filter paper and assayed. The % release of drug was calculated. The observations for different batches are shown in succeeding tables. The percentage release of drug with respect to time for each batch, are graphically show.

As floating dosage form not rotates may not give proper result and also not reproducible results. Similar problem occur with swellable dosage form, as they are hydrogels may stick to surface of vessel or paddle and gives irreproducible results. In order to prevent such problems; various types of modification in dissolution assembly made are as Follows. To prevent sticking at vessel or paddle and to improve movement of dosage form, method suggested is to keep paddle at surface and not too deep inside dissolution medium [29].

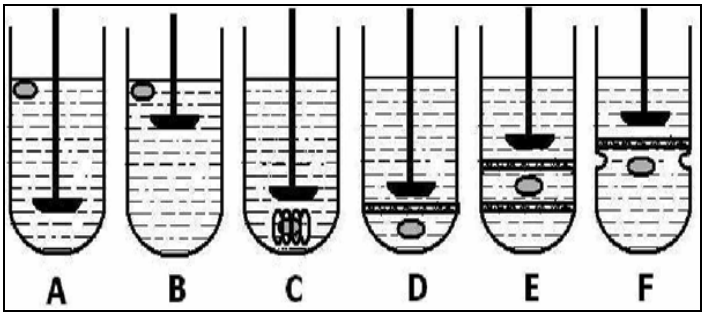
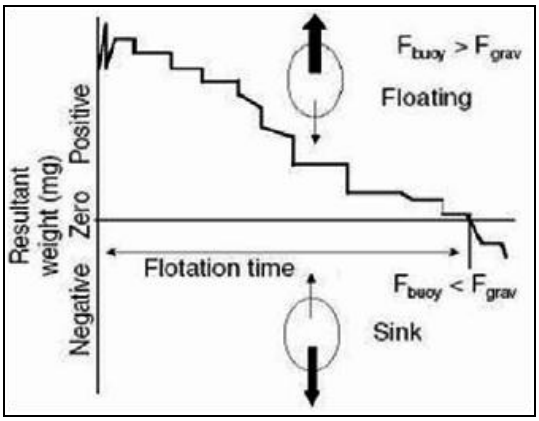


FIG. 6: POSITIONS OF GASTRORETENTIVE DOSAGE FORMS AND ITS DISSOLUTION

As shown in fig. 6:

A. 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.
B. swellable dosage form, as they are hydrogel may stick to surface of vessel or paddle and gives irreproducible results. It is suitable to prevent sticking at vessel or paddle and to improve movement of dosage form inside dissolution vessel.
C. Floating unit can be made fully submerged, by attaching some small, loose, non- reacting material, such as few turns of wire helix, around dosage form. However this method can inhibit three dimensional swelling of some dosage form and also affects drug release.
D. Other modification is to make floating unit fully submerged under ring or mesh assembly and paddle is just over ring that gives better force for movement of unit.
E. Dissolution by placing dosage form between 2 ring/meshes.
F. In previous methods unit have very small area, which can inhibit 3D swelling of swellable units Inspite of the various modifications done to get the reproducible results, so a novel dissolution test apparatus along with modification of Rossett-Rice test Apparatus was proposed [29].

6) **Resultant Weight:** It is necessary to measure the resultant weight as the density changes with change in resultant weight as a function of time. In this some drug is released and simultaneously and some outer part of matrixing polymer may erode out leading to change in resultant weight of dosage form. The magnitude and direction of force/resultant weight (up or down) is corresponding to its buoyancy force (Fbuoy) and gravity force (FgravF) acting on dosage form.



$F = F_{buoy} – F_{grav}$;

$F = (D_f – M/V)gV$

Where,

F = resultant weight of object; D_f = Density of Fluid; DS = Density of Solid object; g = Gravitational force; M = Mass of dosage form; V = Volume of dosage form; So when Ds, density of dosage form is lower, F force is positive gives buoyancy and when it Is Ds is higher, F will negative shows sinking.

7) **Stability:** To assess the stability of the optimized formulation, stability studies were conducted as per the ICH and WHO guidelines. Formulations were packed in HDPE bottles and were kept in the specified temperature and humidity conditions for prescribed duration. At the end of studies, samples were analyzed for the drug content, *in vitro* dissolution, floating behavior and other physicochemical parameters.

8) **Specific Density:** Density can be determined by the displacement method by using Benzene as displacement medium. The density of the system should be less than unity to confer the buoyancy of the system.

9) **Water uptake (for Swelling and Expanding Systems):** It measures swelling property of swellable matrix. Here dosage form is removed out at regular interval and weight changes are determined with respect to time.

Water uptake = WU = (Wt – Wo) * 100 / Wo)

Where, Wt = weight of dosage form at time t; Wo = initial weight of dosage form

10) **Swelling index (for Swelling and Expanding Systems):** As swelling of tablet results in increase in weight and volume of tablet the extent of swelling can be measured in terms of % weight gain by the tablet.

Swelling Index (S.I.) = (Wt-Wo /Wo)

Where, S.I. = Swelling index

Wt = Weight of tablet at time t

Wo = Weight of tablet before placing in the beaker [29].

11) **Mucoadhesive Strength (In case of Mucoadhesive Dosage Forms:** Mucoadhesive strength of the tablet was measured on the modified physical balance. Goat or rat stomach mucosa was used as a model membrane and buffer media 0.1N HCl pH 1.2 was used as moistening fluid. The underlying mucous membrane was separated using surgical blade and wash thoroughly with buffer media 0.1N HCl pH 1.2. It was then tied over the protrusion in the Teflon block using a thread. The block was then kept in glass beaker. The beaker was filled with phosphate buffer media 0.1N HCl pH 1.2 up to the upper surface of the goat stomach mucosa to maintain stomach mucosa viability during the experiments. The one side of the tablet was attached to the glass slide of the right arm of the balance and then the beaker was raised slowly until contact between goat mucosa and mucoadhesive tablet was established.

A preload of 10 mg was placed on the slide for 5 min (preload time to established adhesion bonding between mucoadhesive tablet and goat or rat stomach mucosa. The preload and preload time were kept constant for all formulations. After the completion of preload time, preload was removed from the glass slide and water was then added in the plastic bottle in left side arm by peristaltic pump at a constant rate of 100 drops per min. The addition of water was stopped when mucoadhesive tablet was detached from the goat or rat stomach mucosa. The weight of water required to detach mucoadhesive tablet from stomach mucosa was noted as mucoadhesive strength in grams. From the mucoadhesive strength following parameter was calculated.

$$\text{Force of Adhesion (N)} = \frac{\text{Mucoadhesive strength X } 9.81}{1000}$$

$$\text{Bond strength (N/m}^2\text{)} = \frac{\text{Force of Adhesion (N)}}{\text{Surface area of Tablet (m}^2\text{)}}$$

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

***In-vivo* evaluation:**

1. **Radiology:** It is a simple procedure involving the use of radio-opaque markers, e.g. barium sulphate, BaSO4 is incorporated inside dosage form and X-ray images are taken at various intervals to view GR. Faeces collection (using an automated faeces collection machine and X-ray inspection provide a non-invasive method of monitoring total GI residence time without affecting normal GI motility [29].

2. **Gamma Scintigraphy:** Distribution and retention time of the stomach specific tablets can be studied using the gamma scintigraphy technique ray emitting materials are incorporated into dosage form and then images are taken by scintigraphy. Widely used emitting material is 99Tc. The combination of the sheep model and the gamma scintigraphy method has been proved to be an

extremely useful tool for evaluating the distribution, spreading, and clearance of administered stomach specific tablets [29].

4. **Gastroscopy:** Gastroscopy is done using fiber optics or video systems to inspect visually the effect of prolongation in stomach. It is used for detailed evaluation of GRDDS [30].

5. **Magnetic Marker Monitoring:** Dosage form is magnetically marked with incorporating iron powder inside, and images can be taken by very sensitive bio-magnetic measurement equipment [30].

6. **Ultrasonography:** It is seldomely used because it is not traceable at intestine [30].

7. **^{13}C octanoic acid Breath Test:** ^{13}C Octanoic acid is incorporated into GRDDS. In stomach due to chemical reaction, octanoic acid liberates CO2 gas which comes out in breath. The important Carbon atom which will come in CO2 is replaced with 13C isotope. So time up to which 13CO2 gas observed in breath can be considered as gastric retention time of dosage form. As the dosage form moves to intestine, there is no reaction and no CO2 release [30].

CONCLUSION: Stomach specific drug delivery system offer unique carrier system for many pharmaceuticals and can be tailored to adhere to any mucosal tissue or remain lodged into stomach due to swelling, density or by magnetic means. This gives a signal to extending this approach to improve bioavailability of poorly absorbed drugs in GIT. Designing GRDDS requires a thorough understanding of the physicochemical properties of the drug, the physiological events of the GIT and formulation strategies.

ACKNOWLEDGEMENT: I offer my heartiest thanks and sincere acknowledgement to Mr. R. D. Bendgude (HOD Dept. of Medicinal Chemistry, SVERIs College of Pharmacy), Mr. V.A. Bairagi, Mr. Gangurde A. B. and Mr. D.M. Patil (K.B.H.S.S.T's Institute of Pharmacy, Malegaon). I express my deep sense of gratitude to my parents and well wishers who co-operated me indirectly for the completion of my Work.

REFERENCES:

1. N. K. Jain, Progress in Controlled & Novel Drug Delivery Systems, 1st edition 2004, CBS Publishers, 76-97.
2. S. P. Vyas, Roop K. Khar, Controlled Drug Delivery Concepts & Advances, Vallabh Prakashan, 196-217.
3. AA Deshpande, CT Rhodes, NH Shah, AW Malick. Controlled-release drug delivery systems for prolonged gastric residence: an overview. Drug Dev Ind Pharm 1996, 22, 31–39.
4. NK .Jain. Controlled release and Novel Drug Delivery. 1st edition. CBS publishers and Distributors New Delhi.1997, 353-370.
5. D. M. Brahmankar SB Jaiswal. Biopharmaceutics and Pharmacokinetics A treatise.1995, 337-371.
6. Singh B N and Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention; Journal of Controlled Release 2000, 63: 235-259.
7. Burns S.J., Corness D., Hay G., Higginbottom S, Whelan I.,et al .Development And validation of an *in vitro* dissolution method for a Floating dosage form with biphasic release characteristics. Int. Journal. Pharm; 1995, 121, 37-44.
8. Y.W. Chein, Oral drug delivery and delivery systems, in: Y. W. Chein (Ed. , Novel Drug Delivery Systems, Marcel Dekker, New York, NY, 1992, 139-196.
9. Singh B, Ahuja N 2004. Response surface optimization of drug delivery system. Jain NK, editor. Progress in Controlled and Novel Drug Delivery System. New Delhi, India: CBS Publishers and Distributors, p. 76-97, 470-509.
10. Ritchel WA, Menon A, Sakr A 1991.Biopharmaceutic evaluation of furosemide as a potential candidate for a modified release peroral dosage form. Clinical Pharmacology 13: 629-636.
11. Sangekar, S.; Vadino, W.A.; Chaudhary, I.; Parr, A.; Beihn, R. and Digenis, G. (1987) Int. J.Pharm. 35.
12. Bardonnet, P.L., Faivre, V., Pugh, W.J., Piffaretti, J.C., Falson, F., 2006.Gastroretentive dosage forms: overview and special case of helicobacter pylori. J.Control. Release. 111, 118.
13. Singh BN, Kim, KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release 2000.
14. NK .Jain. Controlled release and Novel Drug Delivery. 1st edition.CBS publishers and Distributors New Delhi.1997, 353-370.
15. C Margeta, BS Sachin. B Debjit, B Bhowmik, B Jayakar. Formulation and evaluation of Controlled release mucoadhesive oral tablet of Clarithromycine. Der pharmacia Lettre; 2009, 1, 83-91.
16. Gupta P.K. and Robinson J.R., Oral Controlled- Release Delivery, in Treatise on Controlled Drug Delivery, A. Kydonieus, Eds., Marcel Dekker, New Jersey, 1992, 255-310.
17. Park K. and Robinson J.R., Bioadhesive Polymers as Platforms for Oral- Controlled Drug Delivery: Method to Study Bioadhesion, Int. J. Pharm. 19 (1 , 1984, 107-127.
18. Park K. and Robinson J.R., Bioadhesive Polymers as Platforms for Oral-Controlled Drug Delivery: Method to Study Bioadhesion, Int. J. Pharm. 19 (1), 1984, 107-127.
19. Klausner, E.A., Lavy, E., Friedman, M., Hoffman, A., 2003. Expandable gastroretentive dosage forms. J. Control. Release 90, 143–162.
20. Caldwell L.J., Gardner C.R., and Cargill R.C., Drug Delivery Device Which Can Be Retained in the Stomach for a Controlled Period of Time, US Patent No. 4735804 (5 April 1988.
21. Gupta P., Vermani K., and Garg S., Hydrogels: From Controlled Release to responsive Drug Delivery, Drug Discov. Today 7 (1), 2002, 569 - 579.

22. J. Timmermans and A. J. Moes, "Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy", J. Pharm. Sci., 1994, 83, 8-24.
23. R. Machida Y., Sannan T., Nagai T., Magnetic granules: a novel system for specific drug delivery to esophageal mucosa in oral administration, Int. J. Pharm. 61 (1-2), 1990 109-117.
24. Hwang S.J., Park H., Park K., Gastric retentive drug delivery systems, Crit. Rev. Ther. Drug Carr. Syst. 15 (3, 1998, 243-284.
25. Desai S, Bolton S. A floating controlled release system: In-vitro – In-vivo evaluation. Pharm. Res. 1993; 10: 1321-1325.
26. V. M. Patel, G. prajapati, M. Patel. Mucoadhesive Bilayer tablets of Propranolol Hydrochloride. AAPS Pharma sci. tech, 2007, 8, 234-242.
27. Timmermans J, Andre JM. Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy. J Pharm Sci. 1994; 83:18Y24
28. Hortor RE, Ross FGM, Darling GH, Determination of the emptying time of the stomach by use of enteric coated barium granules, Br Med J, 1, 1965, 1537-1539.
29. Timmermans J, Andre JM. Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules: new data for reconsidering the controversy. J Pharm Sci. 1994; 83:18Y24.
30. Jao F, Edgren DE, Wang PS, gastric retention dosage form having multiple layers, Int application WO 0038650, 2000.

****