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GASTRO-RETENTIVE DRUG DELIVERY SYSTEM OF ANTIHYPERTENSIVE DRUG

Shashikant Chandrakar[1], Chandrakant Yadav[1]*, Amit Roy[2], Pushpa P. Gupta[3], Riya Vaiswade[1], Ashish Verma[1], Akhilesh Kumar[3]

[1]Department of Pharmaceutics, Columbia Institute of Pharmacy, Tekari, Raipur, (CG), Pin 493111.
[2]Principal and Professor, Columbia Institute of Pharmacy, Tekari, Raipur, (CG), Pin 493111.
[3]Department of Pharmacology, Columbia Institute of Pharmacy, Tekari, Raipur, (CG), Pin 493111.

***Corresponding Author: Chandrakant Yadav**
Department of Pharmaceutics, Columbia Institute of Pharmacy, Tekari, Raipur, (CG), Pin 493111.

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ABSTRACTS
The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. Oral administration has only limited use for important drugs from various pharmacological categories that have poor oral bio-availability due to incomplete absorption and/or degradation in the gastrointestinal tract (GIT). Drugs that are easily absorbed from the gastrointestinal tract (GIT) and have a short half-life are eliminated quickly from the blood circulationso they require frequent dosing to avoid this drawback, the oral sustained-controlled release formulations have been developed in an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the serum for longer period of time. Variousgastro retentive approaches have designed and developed until now, i.e. floating, bio- or mucoadhesive, expandable, unfoldable, super porous hydrogel and magnetic systems. Finally, advantages of gastro retentive drug delivery systems were covered in detail.

KEYWORDS: Gastro-retentive drug delivery system (GRDSs), mucoadhesive system, floating system, swelling, gastric emptying, bioavailability, antihypertensive drugs.

INTRODUCTION
Oral administration is the most suitable mode of drug delivery and is associated with superior patient compliance as compared to other modes of drug intake.[5] Approximately 50% of the drug delivery systems available in the market are oral drug delivery systems which have additional advantages due to patient approval and wellbeing of administration. Gastric emptying of dosage form is already adjustableprocess and its capability to prolong and control the emptying stage is valuable asset for dosage forms, which reside in the stomach for a long duration of time. Several difficulties, are faced in designing controlled released systems for better absorption and improve the bio-availability. Conventional oral dosage forms such as tabletsandcapsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels.[6] Gastro retentive drug delivery system (GRDDS) is useful for enhancing the bioavailability of drug which has lowbioavailability. Drug absorption within the gastrointestinal tract is a quite variable system and it depends upon the elements including gastric emptying technique, gastrointestinal transit time of dosage forms, drug which are absorbed from the gastro intestinal tract (git) and which have short half-life are removed fast from the systemic movement.

Necessity for GRDDs
Traditional oraldeliveryis broadly used in pharmaceutical area to treat diseases. But, conventional transport had many drawbacks and most important draw-lower back is non-site specificity. Some tablets are absorbed at unique site only. They require release at specific site or a release such that maximum amount of drug reaches to the particular site. Pharmaceuticalscienceis now focusing closer to such tablet andcapsules which require site specificity. Gastro-retentive delivery is the uniquedeliverysystem for the delivery of medicines atthe stomachor at the intestine. It is obtained by gastro retentive dosageform into the stomach and a medicine is being liberated at the controlled way to a particular site.

Meritsof gastro retentive drug delivery system
1. Delivery of drugs with limited absorption window in the small intestine region.
2. Longer residence time in the stomach could beadvantageous for local action in the upper part of the smallintestine, for example treatment of peptic ulcer disease.

3. Improved bio-availability is expected for drugs that areabsorbed readily upon release in the GI tract such ascyclosporine, ciprofloxacin, ranitidine, amoxicillin, captopril, etc.
4. Patient compliance by making a once a day therapy.
5. Improved therapeutic efficacy.
6. Reduces frequency of dosing.
7. Targeted therapy for local ailments in the upper GI tract.
8. Bioavailability of the therapeutic agents can beconsiderablyimprovedparticularly those whichmetabolized in the upper part of GItract.
9. Gastro-retentive drug delivery can be formulated as prolong andcontrolledreleasedosage form, which purposeseffectivetreatment in stomach. They arebeneficial in the treatment of diseases related to the stomach and small intestine.

Hypertension and its therapy

Hypertension is the term which is used to characterised elevation of blood pressure. Pulse rate is normally beneath 120/80 mmHg; Blood Pressure between 120/80 mmHg and 139/89 mmHg is classified "pre-hypertension", and a Blood Pressure of 140/90 mmHg or above is viewed as high. An elevation of the systolic or potentially diastolic blood pressure increase the risk of enhancing cardiac disease, renal disease, Atherosclerosis or arteriosclerosis and brain damage. These difficulties of hypertension are frequently referred to as end-organ harm because harm of these organs is the result of chronic high blood pressure. Determination of hypertension is significant so that efforts can be made to normalized blood pressure and prevents complication. Antihypertensive therapy seeks to prevent complication of high BP such as stroke and myocardial information.

WHO hypertension facts: Globally, nearly 1 billion people have high BP of these two third are developing countries. Hypertension is one of the most important cause of premature death worldwide & the problem is growing. Hypertension kill nearly 8 million people every year worldwide & nearly 1.5 million people each year in the south east Asia, approximately one third of adult population in the south east Asia region has high Blood pressure.

Hypertension and Pregnancy

The use of anti-hypertensive in pregnancy must consider foetal well-being. Treating uncomplicated Stage 1 hypertension is often not necessary in otherwise low-risk women with normal renal function and no other target organ disease. These women should be closely followed during pregnancy. Pre-eclampsia or other pregnancy-induced hypertension should be treated by a physician experienced in managing these diseases. Women considering pregnancy, who are hypertensive and require treatment, should be on anti-hypertensive medication ideally three to six months prior to conception. Medications for treating significant hypertension during pregnancy, in order of preference are:

1) Methyldopa – the drug with the longest experience and probably still most commonly used. Problems with this UMHS Hypertension Guideline, February 2009 13 medication includes frequent side effects and the need to dose multiple times a day.
2) Beta-blocker with or without diuretic (avoiding Atenolol, which may be associated with intrauterine growth retardation) – are relatively popular and the first choice of some.
3) Labetalol
4) Calcium channel blockers
5) Diuretics are also acceptable to use
6) Contraindicated in pregnancy are ACE inhibitors, ARBs, and Renin inhibitors.

Anatomy of stomach

The stomach has 4 most important sections. The main function of fundus or body is storing, while that of cardiac is mixing or grinding. The fundus regulates the elevated volume all through consuming by means of rest of the fundus muscle fibres. The fundus also employs a consistent pressure at the gastric contents persistentbythe distal stomach, to bypass via the pyloric valves into small intestine, particles have to be in size of one to two mm called chime anatomy of stomach.

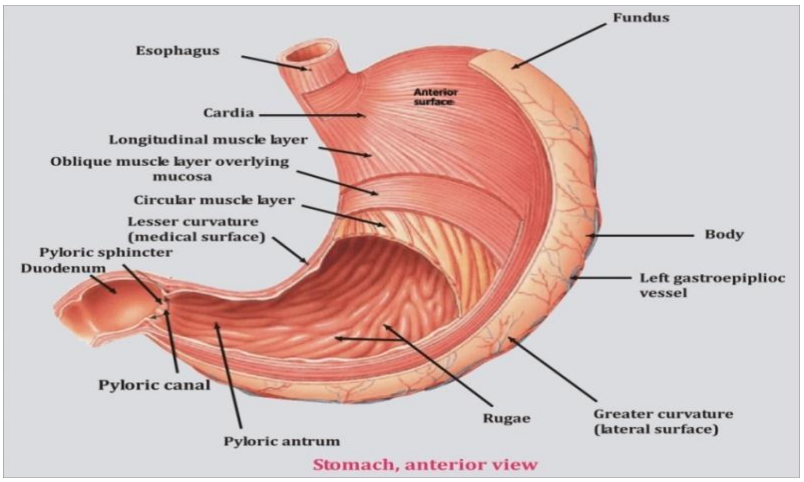

Fig. Stomach, anterior view.

Factors affecting gastric retention

Gastric residence time of oral dosage is affected from numerous factors.

1. Extent of meal: the larger the quantity of meal, the longer could be gastric emptying time.
2. Composition of meal: fat promote the secretion of bile, which has an inhibitory impact on gastric emptying time.
3. Physical state of meals and dosage form: viscous material empties slowly than much lesser viscous materials.
4. Exercise: slow down the gastric emptying time.
5. Emotion: anxiety and tensions promotes gastric motility in which as depression slow down it.[7]

Criteria for choice of drug candidate for GRDDS

The Gastro retentive drug deliverysystem is suitable for following type of drugs

1. Tablets are regionally active inside stomach e.g. antacids, misoprostol, etc.
2. Drugs that have limited absorption window in Git tract forinstance, para-aminobenzoic acid, levodopa, riboflavin, furosemide, and so on.
3. Drugs which can be unstable inside the abdominal and in colonic environment, drugs likeranitidine, captopril, and metronidazole.
4. Drugs that disturb regular colonic microbe example antibiotics towards helicobacter pylori.
5. Drugs that show low solubility on high pH values example verapamil, diazepam, chlordiazepoxide.[9]

Limitations of GRDDS

1. Requirement of high raise of fluids in stomach for delivery system to glide and work correctly.
2. Requires the presence of meals to postpone gastric emptying.
3. Tablets, which undergo great first by pass metabolism, won't be appropriate applicants for floating drug delivery system for the reason that slow-moving gastric emptying.

Factors affecting gastro retentive drug delivery system

Density: dosage form resistance is due togastric retention time,which is dependent on density.

Size: Dosage form units with diameter more than 7.5 mm are stated to growth gastric residence timerelated with those with a diameter of 9.9mm.

Shape: Tetrahedron and ring-shaped with flexural modulus of 48 and 22.5 kgconsistent with square inch (KSI) are suggested to show a better GRT and a 100% retention at 24 hours related with different shapes.[9,10]

Single or multiple unit formulation: More than one unit formulations exhibit a greater predictable release profiles and insignificant impairment of performance, allow co-administration of devices with different release profiles or encompassing incompatible substances and allow a bigger margin of safety with reference to dosage form failure in comparison withsingleunit dosage form.

Nature of the meal: Intake of heavy polymers or fatty acid salts can exchange motility outline to the stomach of fed stage, therefore reducing the gastric emptying charge and prolonging drug release.[11]

Caloric content: Gastric retention time can be increased by using 4 to 10 hour with a meal,it is high in proteins and fats.[12]

Frequency of feeding: The gastric retention time can growth by way of over 400 minute when consecutive food is given in comparison with only meal due to the low frequency.

Age: Aged humans, in particular the ones over 70, have significantly longer gastric retention time.

Posture: Retention time can differ among supine or upright ambulatory affected person states.

Gastric Concomitant drug administration: Anti-cholinergic, like atropine and propantheline, opiates like codeine and prokinetic marketers like metoclopramide and cisapride, affect the floating drug delivery system.

Biological factors: Diabeteshas an effect on the floating drug delivery system.

Approaches to gastric retention: Numerous attempts have been made to hold the dosage form within the stomach as a way of expanding the retention time. Those tries encompass introducing floating dosage forms (gas producing system), swelling and mucoadhesive system. Excessive density structures, modified shape system. Gastricemptying delaying tricks and co-administration of gastric delaying medicines, among these, the floating dosage forms had been used maximum generally.

Floating drug delivery system, with low density provided that enough buoyancy to flow over the gastric subjects, bio adhesive systems, allowing the localized retaining of the system within the stomach, swelling and increasing systems, counteracting transit from the gastric sphincter, excessive density system, enduringwithin the stomach for longer time period by way of sedimenting to the folds of stomach.

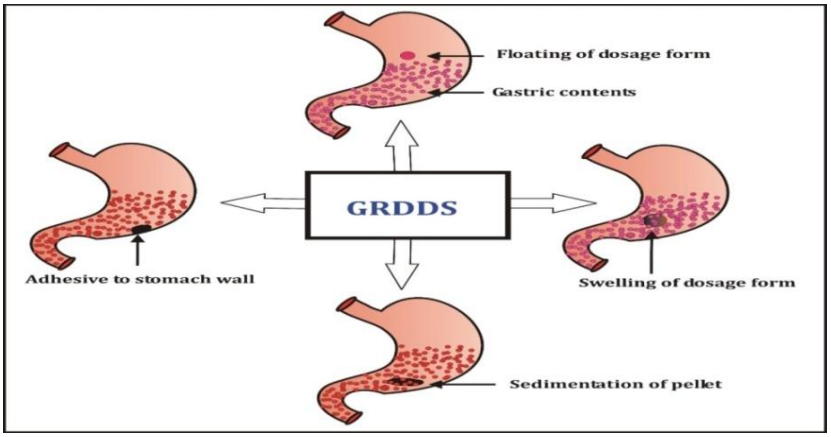

Figure: Approaches to gastric retention.

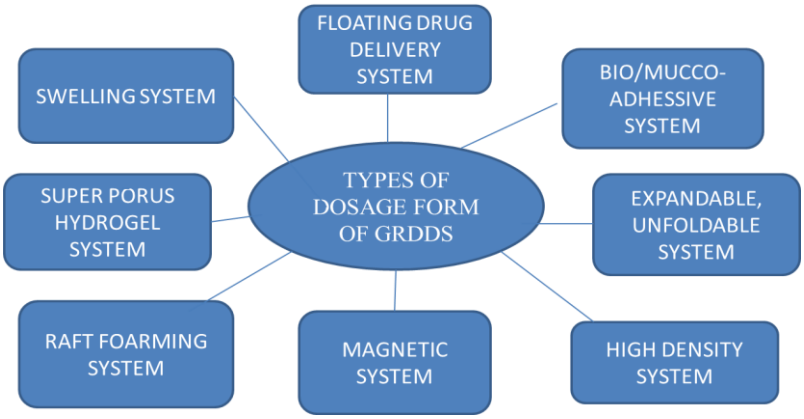

Figure: Types of GRDDS.

Types of gastro retentive dosage form

A. Floating systems 10[13]: Floating system isthe low-density system that has enough buoyancy to flow over the gastric substances and continue to be inside the stomach for extended duration. Even as the system flow over the gastric subjects, the drug is liberated slowly on the preferred rate which leads to elevated GRT and variability decreases in plasma drug concentration. The fdds and bio adhesive drug delivery are widely used method for gastro retention and floating systems. Floating system can also be categorized such as effervescent or non-effervescent systems.

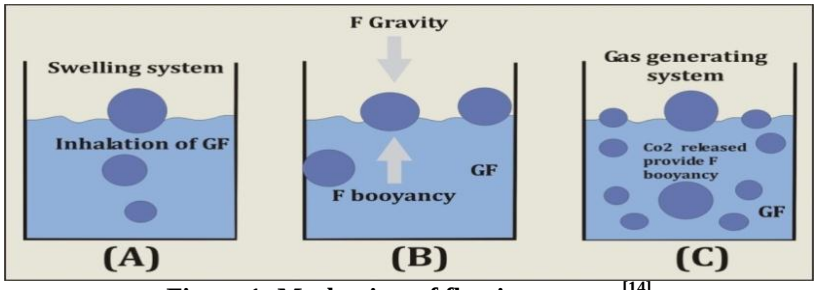

Figure 1: Mechanism of floating system.[14]

I. Effervescent systems: the drug delivery system which floats inside the stomach is full of vacuum, air, and an inert gas. Gas may be brought in the floating chamber with the aid of the volatilization of organic solvent (example:-ether or cyclopentane) or via the carbon dioxide produced as an outcome of an effervescent reaction among organic acids and carbonate–bicarbonate salts. These devices comprise a hollow deformable unit that converts from a collapsed to an elevated position.

a) Volatile liquid containing systems: This type of systems contains two chambers separated through an impermeable, strain-responsive, portable bladder. The primary chamber consist the drug and the secondary chamber carries the volatile liquid. The gastric retention time of drug delivery system may be sustained by means of included inflatable chamber, which consist liquid likecyclopentane, ether. Thatgasifiesbody temp to produce the infloatation of chamber in to the stomach.

b) Gas generating system: Floatability also can be achieved with the production of gas bubbles. Co_2can be generated in situ by means of the incorporation of carbonates or bicarbonates, which react with acid- both

the natural gastric acid or co-formulated as citric acid or tartaric acid. Stoichiometric ratio of sodium bicarbonate or citric acid for gas production technology is said to be 1:0.76.

I. Non effervescent systems[12,15]: Non-effervescent system include a high degree (20–75 % w/w) of one or greater gel-forming, tremendously swellable, cellulosic hydrocolloids (example: hydroxypropyl cellulose, hydroxyl ethylcellulose, hydroxypropyl methylcellulose (hpmc), or sodium carboxymethyl cellulose), polysaccharides, or matrixforming polymers (example, polyacrylates, polycarbophil and polystyrene) into capsules or tablets.Upon interaction with gastric fluid, these gel formers, polymers hydrate or polysaccharides and forms colloidal gel barrier that regulates the rate of fluid permeation into the device and consequential drug release.

a) Hydrodynamically balanced systems OR Colloidal Gel Barrier System: These system is single unit dosage form, containing one and extra gel arising hydrophilic polymers, hpmc are mostly used excipient, althoughsodium carboxymethyl cellulose,alginic acid and agar are also used. The polymer is integrated with drug and normally administered into gelatine capsule. The capsules promptly dissolve inside the gastric fluid, and hydration and swelling of the surface polymer produces a floating mass. Drug release is managed by way of the formation of hydrated boundary at the surface.

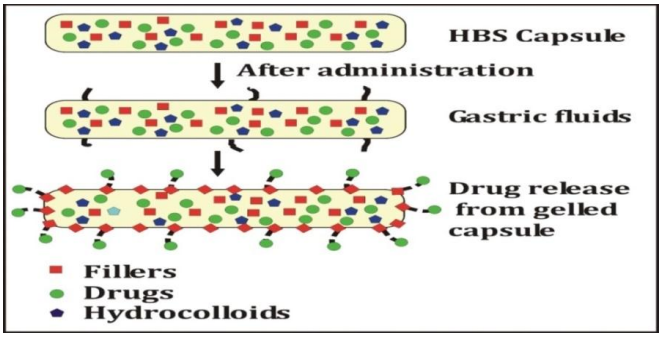

Fig: Hydrodynamically balanced system.

b) Micro porous compartment system: This technology is based on the encapsulation of a drug reservoir inside a micro porous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the un-dissolved drug. In the stomach, the floatation chamber contains trapped air that causes the delivery system to float over the gastric content.

c) Alginate bead: Multi-unit floating dosage forms have been developed from freeze calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride. Causing the precipitation of calcium alginate. The beads are than separated, snap-frozen in liquid nitrogen and freeze-dried at 400C for 24 h, leading to the formation of a porous system.

d) Micro balloons or Hollow Microspheres 14.(16): Micro balloons / hollow microspheres loaded with drugs in their other polymer shelf were prepared by simple solvent evaporation or solvent diffusion / evaporation methods.[38] (Figure 1) to prolong the gastric retention time (GRT) of the dosage form.

B. Bio/mucoadhesive systems: Bio adhesive drug delivery systems (bdds) are used as a transport tool within the lumen to improve drug absorption in a site particular way. This technique involves the use of bio adhesive polymers that may adhere to the epithelial or epithelial cell surface mucin within the stomach. It increases the GRT bygrowing the intimacy and period of contactamongthe dosage shape and the biological membrane.

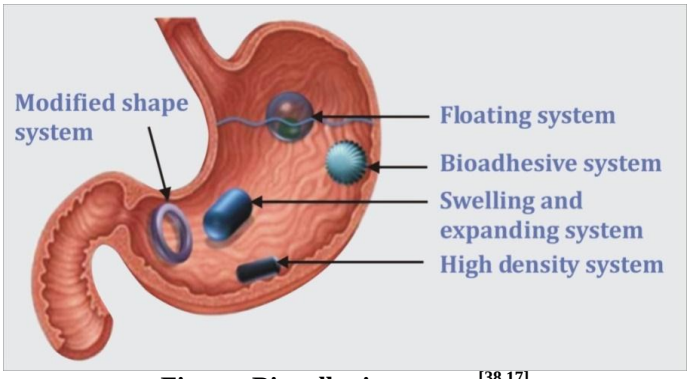

Figure: Bio adhesivesystem.[38,17]

Basic mechanisms of adhesion

Wetting theory, which is predominantly based at the capability of bio adhesive polymers to spread and grow intimate contact with the mucous films.

1. The diffusion principle which proposes physical entanglement of mucinstrands the flexible polymer chains, or an interpenetration of mucinstrands into the porous structure of the polymer substrate.
2. Absorption theory, recommends that bio adhesion due to the secondary forces which includes hydrogen bonding and vanderwaals forces.
3. Electron theory, thatrecommendsattractive electrostatic forces among the glycoprotein mucin network and bio adhesive material.

Binding of polymers to the mucin/epithelial surface may be divided into 3 classes

Hydration – mediated adhesion: Some hydrophilic polymers havingaffinity to imbibe large quantity of water and get sticky, thereby obtaining bio adhesive properties. The extended gastro retention of the bio/mucoadhesive delivery system is in addition managed with the aid of the dissolution rate of the polymer.

Bonding –mediated adhesion: The adhesion of polymers to a mucus or epithelial cell surface includes several bonding mechanisms which include physical, chemical and mechanical bonding. Chemical bonds may be either covalent or ionic in nature. Secondary chemical bonds include dispersive interactions (i.e. vanderwaals interactions) and more potent definite interactions along with hydrogen bonds. The hydrophilic functional agencies accountable for forming hydrogen bonds are the hydroxyl and carboxylic groups.[18]

Receptor – mediated adhesion: Several polymers having capacity to bind specific receptor sites at the cell surface. The receptor mediated times serves as a capability method in bio/muco- adhesion, therefore improving the gastric retention of dosage forms. Severalplant lections, like tomato lections, engage specially with the sugar groups found in mucus or at the glycocalyx.[19]

C. Expandable, unfoldable and swellable systems:[20,21]A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However,the dosage form must be small enough to beswallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations are required to developan expandablesystem

System to prolong gastric residence time

1. A small configuration for oral intake,
2. An expanded gastro retentive form, and
3. A final small form enabling evacuation following drug release from the device.

D. High-density systems: Those systems, having density of ~3 g, are retaining the rugae of stomach are able to bear up its peristaltic movements.Overhead threshold density of 2.4–2.8 g, such system may be retaining lower part of the stomach.

E. Magnetic Systems: This method is used to improve the gastric retention time is primarily based at the easy principle that dosage form includes a small inner magnet, or a magnet positioned on the abdomen above the perception of the stomach. While magnetic system appears to work, the outside magnet should be located with degree of precision that could compromise patient compliance.

F. Raft-Forming System: Raftsystems comprise alginate gels those have carbonate factor and, upon consequences with gastric acid, bubbles form in gel, allowing floating. The mechanism comprises the development of glutinous cohesive gel in contact with gastric fluids, whereinto each part of the liquid swells and developcontinuous layer referred to as a raft. This raft flows on gastric fluids since low bulk density formed by the development of Co_2.

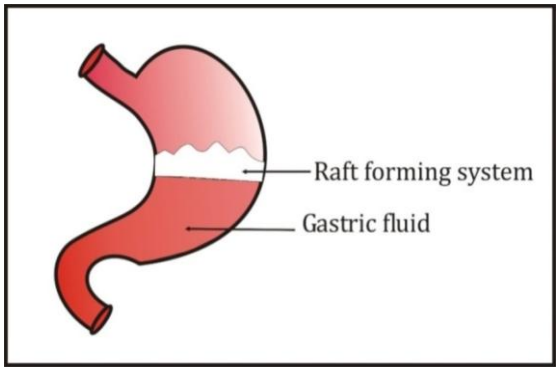

Fig: Raft forming system.

G. Super porous Hydrogels[22]**:** Although these are swellable systems, they differ sufficiently from the conventional types to warrant separate classification with pore size ranging between 10 nm and 10µm. Absorption of water by conventional hydrogel is very slow process and several hours may be needed to reach an equilibrium state during which premature evacuation of the dosage form may occur. Super porous hydrogel, average pore size > 100 µm, swell to equilibrium size within a minute, due to rapid water uptake by capillary wetting through numerous interconnected open pores. Moreover they swell to a large size (swelling ratio 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contractions. This is achieved by a co-formulation of a hydrophilic particulate material, Ac-Di- Sol (crosscarmellose sodium).

H. Swelling systems[23]**:** After being swallowed, those dosage forms swell to a length that stops their passage by the pylorus. Asa outcome, dosage form is retaining inside stomach for extended time period. Thesesystemsare certain time denoted as plug type systembecausethey have tendency to stay lodged at

pyloric sphincter. These polymeric matrices stay within the gastric hollow space for some hours even within the fed state. Sustained and controlled drug release could be achieved by means of selecting a Polymer with the right molecular weight and swelling properties.

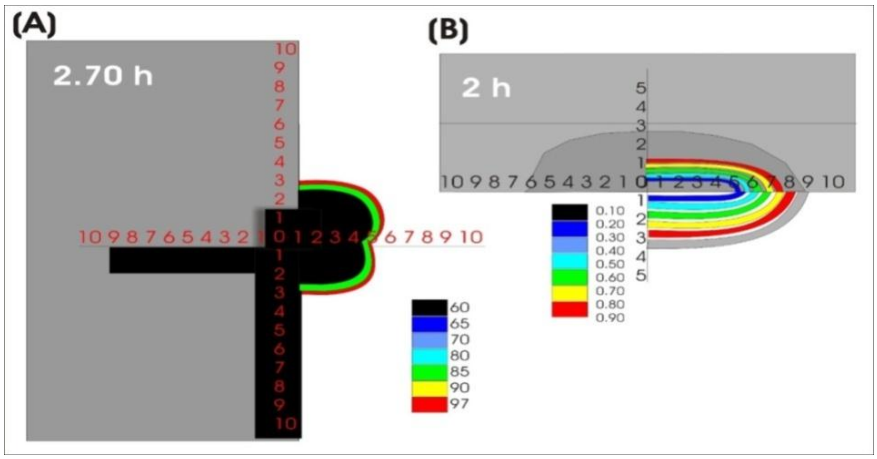

Figure: Swelling system.

Table I:-The commercial dosage forms of antihypertensive drugs.

Drugs	Polymer	Reference
Losartan	HEC	Chen 2010 et al.
Propranolol	Chitosan	Chinta 2009, Srikanth et al.
Furosemide	(HPMC) Hydroxypropyl methyl cellulose	Ozedmir N. 2000 et al.
Verapamil	HPMC, EC, Carbapol	Elkheshen SA. 2004 et al.
Captopril		Martinez IJ.2010 et al.
Quinapril	HPMC K4M, Carbapol 940.	MaliAD., Bathe RS. 2015 et al.
Lisinopril	HPMC K4M	Semwal R. Smwal RB. 2014 et al
Metoprolol	HPMC K100M, HPMC K15	Ratnaparkhi MP. Garje PK. 2013 et al.
Nimodipin	HPMC, PEG, PVP	Barmpalexis p. Kachrimains K. 2011 et al
Amlodipine	HPMC E50, HPMC K100, EC	Ramasubramaniyam p. 2013 etal.
Atenolol	HPMC K15M	Charan DV. Meher CP.2013 et al
Diltiazem	HPMC, Eudragits, Lactose	Boyapally h. Nukala R. , 2009 et al.
Nefidipine	HPMC K100M	N.Shaikh, S.A. Payghan 2018 et al.
Carvedilol	P0laxamer, C-P40, Xanthan Gum, PVP	Venkatasrikanthmekha 2014 et al
Labetalol	HPMC K4M, HPMC K100M, Polaxamer M127.	Harshal Garse, Rajashreehirleker, 2010 et al.

CONCLUSION

Good enough control of the gastric residence time combined with controlled drug release patterns can significantly enhance the bioavailability of the drug. To gain this goal, floating, bio adhesive, expanding/ swelling and raft forming systems have depicted promising ability. However, several different structures want to be explored for reaching most therapeutic efficacy. A controlled drug delivery system along with prolonged gastric retention may have great practical importance for the medicine whichhave slight absorption window inside upper small intestine.

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