# A Review on Gastroretentive Drug Delivery Systems for Antidiabetics and Its Present Status

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**Abstract: The present review provides concise information on status of gastro-retentive drug delivery systems for antidiabetic molecules. Present review emphasis on pharmacotherapy of diabetes via gastric retention of drug molecules. The gastro-retentive system is a proven useful tool for sustaining the drug release for the drugs having good absorption through the GIT, drugs with narrow therapeutic index and low dose drugs. The gastro-retentive dosage forms have also been developed for antidiabetic molecules and metformin hydrochloride, the first line drug in the treatment of diabetes is commercially available in the market in the form of sustained release formulations. As oral antidiabetic therapy is required for prolonged duration, the oral hypoglycemic may lead to side effects such as diabetic neuropathy, diabetic myopathy and many more. The primary reason for side effects is under-utilization of the drug molecule which can be improved using gastro-retentive drug delivery systems thereby minimizing the side effects. Despite being one of the most successfully systems, the commercial value gastro-retentive drug delivery systems is still below par. Gastro-retentive drug delivery systems for antidiabetic drug molecules are still awaited. The research is still in progress for gastro-retentive formulations which can attract industry utilizing these systems for humanely causes.**

**Keywords: Gastro-retentive drug delivery systems, Antidiabetic, Diabetes, Gastric retention, GIT, Absorption, Therapeutic index, Hypoglycemic.**

## I. INTRODUCTION

Oral route of administration has benefits such as low treatment costs and ease of administration, high level of patient conformity and so far remain the preferred route of administration. However drug absorption from oral route is not always uniform due to the physiological factors and gastrointestinal (GIT) system heterogeneity. Moreover, many involuntary variables influence drug uptake throughout the GIT such as variable pH, intestinal flora, gastrointestinal transit time, gastric secretions and absorption surface area. The traditional immediate release drug delivery systems are not able to combat the problems associated with low drug absorption in the gastrointestinal transit as these systems do not possess any additional characteristics to counter stomach motility and thus are not suitable for the drugs which are to be absorbed in the upper part of GIT.

Incomplete drug deliverance and subsequent reduction in bioavailability are the consequence that can be ascribed for the failure of traditional devices. To overcome these issues, drug delivery systems that can control drug release and the residence time of the drug have been developed. Such systems are designed to reside in the upper GIT for a long period of time during which they regulated the release of the drug. The longer contact time with absorbing membrane of the gastro-retentive systems permits greater site absorption and greater bioavailability of drugs. These systems are successfully developed and scaled up for commercial use. Additional benefits of gastro retentive drug delivery systems include:

1. Improved therapeutic effect for low-solubility drugs due increased drug solubility and absorption from stomach
2. Reduction in drug dose and
3. Reduction in associated side effects.

### 2.1 Anatomy and physiology of stomach:

Success of GRDDS relies on the understanding of stomach physiology and related gastric emptying process. Structurally the human stomach is composed of three anatomical regions: fundus, body and pylorus, as depicted in Fig. 1. After a meal, the average volume

of a stomach is about 1.5 l, which varies from 250 to 500 ml during the inter-digestive phase.

The part made of the fundus and the body acts as a reservoir of any undigested material, while the pylorus performs as the principal site for the mixing action. Being the lower part, the pylorus works as a pump for gastric emptying by a propelling action. Pylorus acts to separate the stomach from the duodenum and plays a major role in gastric residence time of the ingested materials. However, the pattern of the gastric motility is different for the fasting and fed state. The gastric motility pattern is systematized in cycles of activity as well as quiescence. The duration of each cycle is 90–120 min and it contains four phases, as mentioned in Fig. 2. The motility pattern of the stomach is usually called migrating motor complex (MMC). [19]

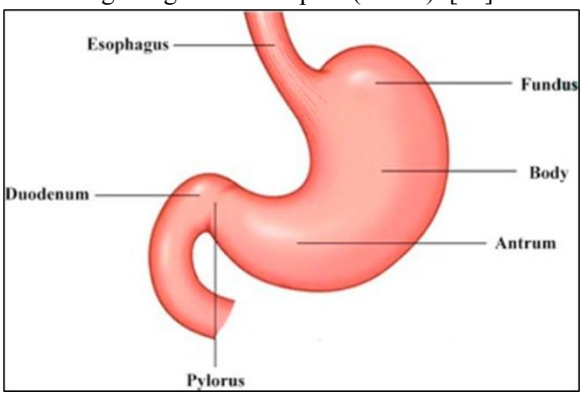


Fig. 1. Diagram of human stomach.

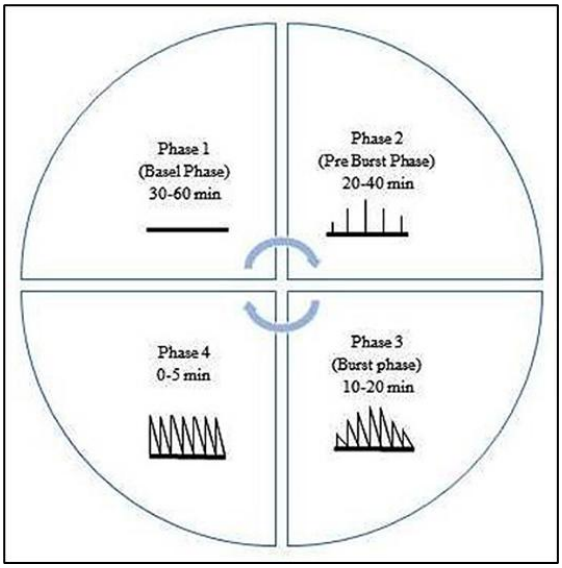


Fig. 2. Motility pattern in gastrointestinal tract

2.2 Gasrtoretentive drug delivery systems:

Gastro-Retentive Drug Delivery System (GRDDS) has gained immense popularity in the field of oral drug delivery recently. It is a widely employed approach to retain the dosage form in the stomach for an extended period of time and release the drug slowly that can address many challenges associated with conventional oral delivery, including poor bioavailability. Different innovative approaches like magnetic field assisted gastro-retention, plug type swelling system, mucoadhesion technique, floating system with or without effervescence are being applied to fabricate GRDDS. [19]

Gastro-retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose. To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drugs that are less soluble in a high pH environment. Also prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer, etc.

2.2.1. Advantages of GRDDS:

1. Enhanced bio-availability.
2. Reduced frequency of dosing.
3. Targeted therapy for local ailments in the upper GIT.
4. Patient compliance.
5. Improved therapeutic efficacy.

Gastro-retentive drug delivery system (GRDDS) greatly improves pharmacotherapy of the stomach through local drug release leading to high drug concentrations at gastric mucosa (eradicating helicobacter pylori from the sub-mucosal tissue of the

stomach), making it possible to treat stomach and duodenal ulcers, gastritis and esophagitis, reduce the risk of gastric carcinoma, controlled release antacid formulations. GRDDS can be used as carriers for drugs which are absorbed from absorption windows in stomach. For example, various antibiotics, antiviral and antifungal agents etc. (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines, etc.) are taken up only from very specific sites of the GI mucosa.

2.2.2 Disadvantages of GRDDS

There are certain situations where gastric retention is not desirable. Aspirin and nonsteroidal anti-inflammatory drugs are known to cause gastric lesions and slow release of such drugs in the stomach is unwanted. Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastro-retentive systems. Furthermore, other drugs such as; isosorbide dinitrate that are absorbed equally well throughout the GIT will not be suitable for incorporation into a gastric retention system.

Also, GRDD's have some limitations such as:

1. Requirement of high levels of fluids in stomach for the delivery system to float and work efficiently.
2. Requires the presence of food to delay gastric emptying.
3. Drugs, which undergo significant first pass metabolism, may not be desirable candidates for floating drug delivery system since the slow gastric emptying.
4. May lead to alter systemic bioavailability.
5. Drugs having solubility or stability problems in the highly acidic gastric environment or which are irritants to gastric mucosa cannot be formulated as GRDDS.

2.2.3 Factors Controlling Gastric Retention of Dosage Forms:

(a) Density of Dosage Form:

- Dosage forms having a density lower than that of gastric fluid experience floating behaviour and hence gastric retention.
- A density of <I.O gm/ml is required to exhibit floating property.
- However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium.

(b) Shape and Size of the Dosage Form:

- The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units.
- In most cases, the larger the dosage form the greater will be the gastric retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine.
- Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes.

(c) Food Intake and Nature of Food:

- The presence or absence of food in the stomach influences the GRT of the dosage form.
- Usually, the presence of food increases the GRT of the dosage form and increases drug absorption by allowing it to stay at the absorption site for a longer time.

(d) Effect of Gender, Posture and Age:

- Generally, females have slower gastric emptying rates than male.
- The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state.
- In case of elderly persons, gastric emptying is slowed down.

2.2.4 Approaches for GRDDS

1. Floating drug delivery systems.
2. Mucoadhesive systems.
3. Swellable systems.
4. High density systems

2.2.5. Classification for GRDDS:

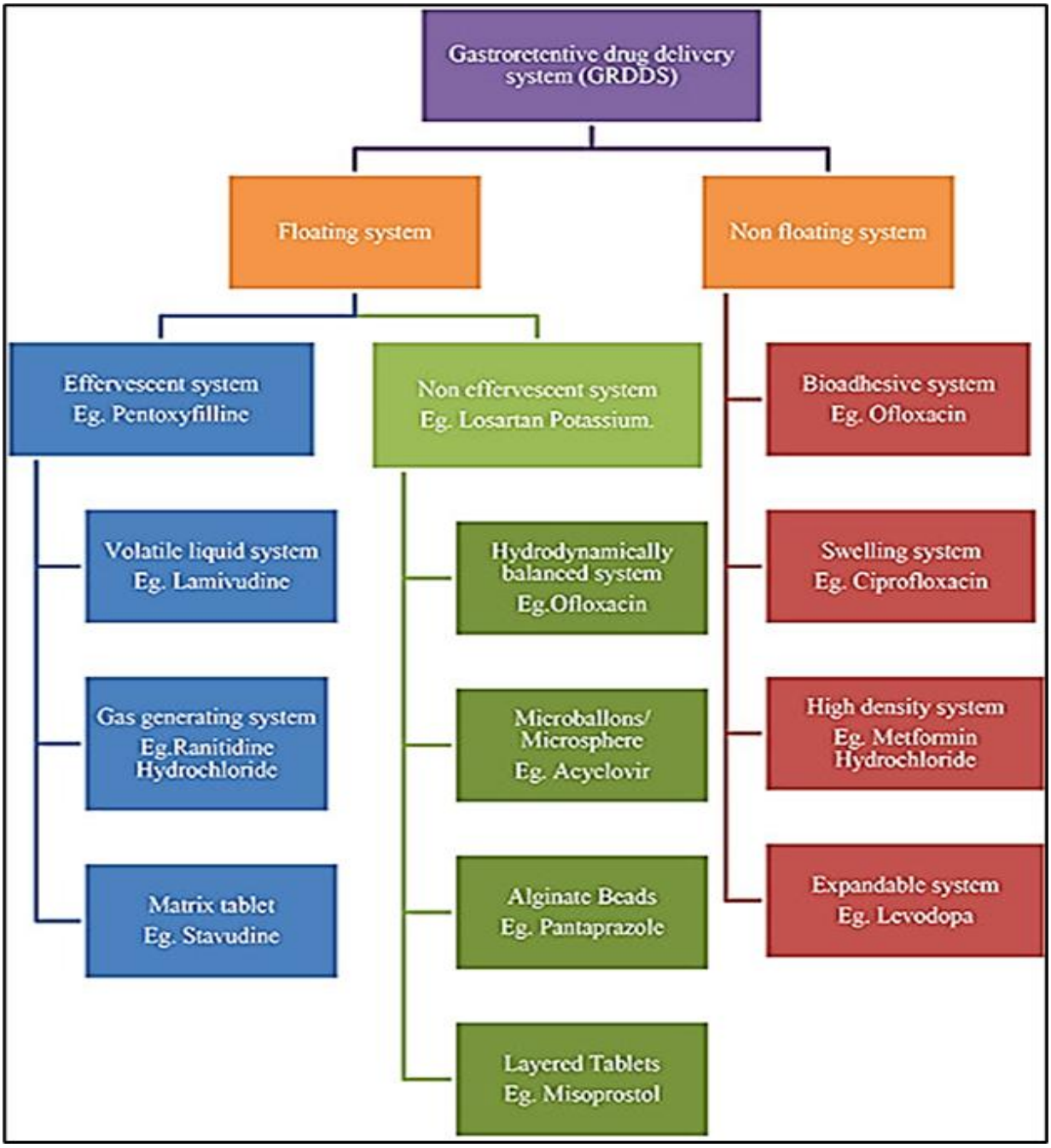


Table-1: Classification of GRDDS

2.2.5.1. Floating Drug Delivery System

Floating drug delivery systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system floats on gastric contents, the drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This results in an increase in gastric retention time and a better control of fluctuations in plasma drug concentrations. Floating systems can be classified into two distinct categories, (i) Effervescent and (ii) Non-effervescent systems.

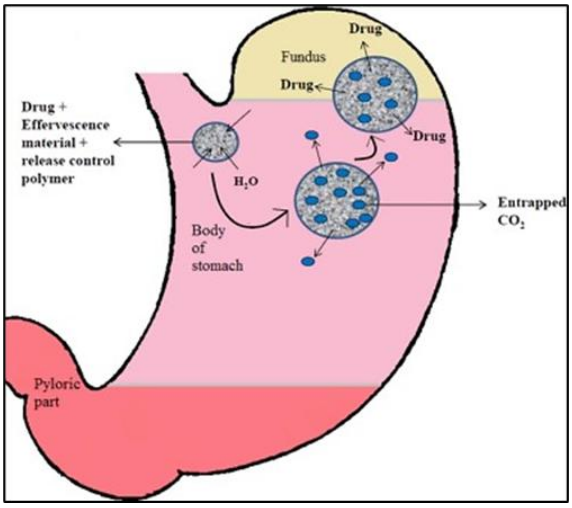


Fig. 3. Floating drug delivery systems (FDDS):

(i) Effervescent:

a) Gas generating systems.
b) Volatile liquid containing systems.
c) Inflatable gastrointestinal delivery systems.
d) Intragastric osmotically controlled drug delivery system.

(ii) Non-Effervescent:

a) Colloidal gel barrier systems.
b) Alginate beads.
c) Hollow microspheres.
d) Microporous compartment system.

(i) Effervescent:

(a) Gas Generating Systems:

Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS):

These are as shown in Fig. 3.16 and formulated by intimately mixing the C02 generating agents and the drug within the matrix. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release, the residual system is expelled from the stomach. This leads to an increase in the gastric retention time and a better control over fluctuations in plasma drug concentration.

(b) Volatile Liquid / Vacuum Containing Systems:

Intragastric Floating Gastrointestinal Drug Delivery System:

These systems can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporous compartment.

(c) Inflatable Gastrointestinal Delivery Systems:

In these systems, an inflatable chamber is incorporated, which contains liquid ether that evaporates at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration, the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in the stomach. The drug continuously released from the reservoir into the gastric fluid.

d) Intragastric Osmotically Controlled Drug Delivery System:

It is comprised of an osmotic pressure-controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that vaporizes at body temperature to inflate the bag. The osmotic pressure-controlled drug delivery device consists of two components drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi-permeable housing. In the stomach, the water in the gastro-intestinal fluid is continuously absorbed through the semi-permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag which forces the drug reservoir compartment to reduce its volume and which in turn activate the drug release from the drug solution compartment through delivery orifice. The floating support is also made to contain a bio-erodible plug that erodes after a

predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach.

(ii) Non-Effervescent:

(a) Colloidal Gel Barrier Systems:

- Such systems contain drug with gel forming hydrocolloids meant to remain buoyant on stomach contents.
- These systems incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids. For e.g. HPMC, NaCMC.
- On coming in contact with gastric fluids forms a viscous core.
- Incorporates 1-120 and entraps air.
- Density of system falls below 1 gm/cm $^3$. Then it starts floating.

(b) Microporous Membrane System:

Based on the encapsulation of drug reservoir inside a Microporous compartment,

- The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug.
- In stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents.
- Gastric fluid enters through the apertures, dissolves the drug and carries the dissolved drug for absorption.

(c) Alginate Beads:

- 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.
- Sodium alginate + Calcium chloride, Calcium alginate + NaCl.
- The beads are then separated and frozen in liquid nitrogen, and freeze dried at -40$^0$ C for 24 hours, leading to the formation of porous system.
- Maintain a floating force of over 12 hours.

**(c)** Hollow Microspheres:

- Microballoons / hollow microspheres loaded with drugs are prepared by simple solvent evaporation method.
- Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and pectin, etc.
- These systems have capacity to float on acidic dissolution media containing surfactant for about 12 hours invitro.

2.2.5.2. Bioadhesive or Mucoadhesive Drug Delivery Systems

Bioadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bio-adhesive polymers are used and they can adhere to the epithelial surface in the stomach.

Thus, they improve the prolongation of gastric retention. The basis of adhesion is that, a dosage form can stick to the mucosal surface by different mechanisms. These mechanisms are:

1.. The wetting theory, which is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.

2.The diffusion theory, which proposes physical entanglement of mucin strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.

3.The absorption theory, suggests that bio-adhesion is due to secondary forces such as; vander Waal forces and hydrogen bonding.

4.The electron theory, which proposes attractive electrostatic forces between the glycoprotein mucin network and the bio-adhesive material.

Materials commonly used for bioadhesion are poly acrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol (PEG) and polylactic acids, etc. Even though some of these polymers are effective at producing bioadhesive, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract (GIT).

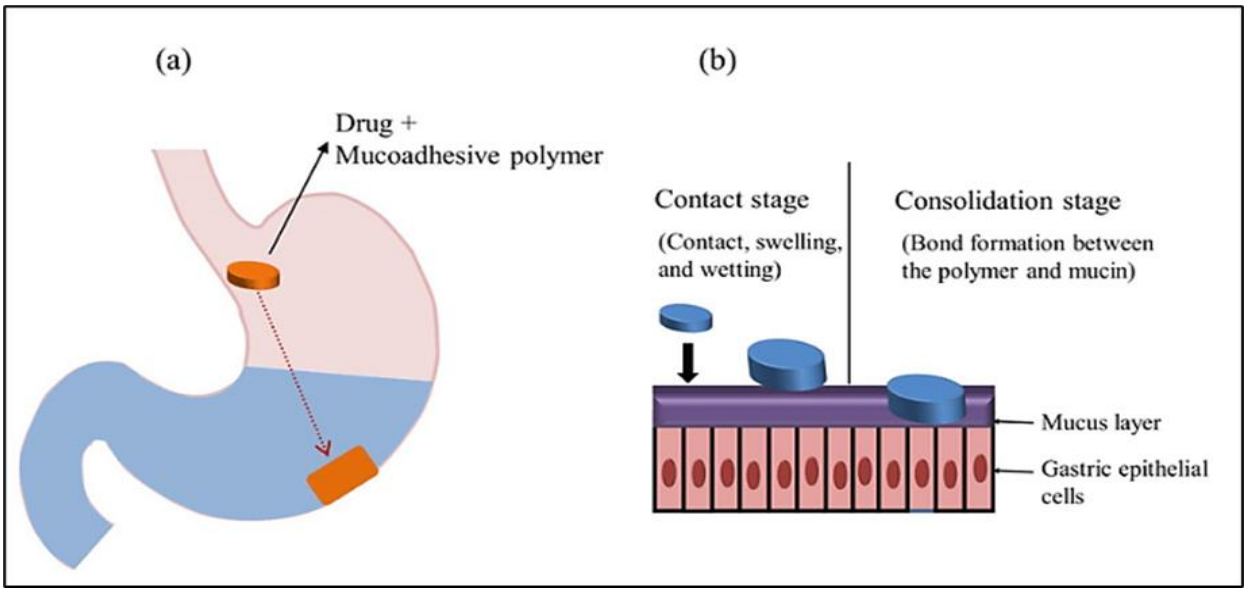


**Fig. 4. Mucoahesive drug delivery systems**

2.2.5.3. Expandable, Unfoldable and Swellable Systems

A dosage form in the stomach will withstand gastric transit if it is bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations are required to develop an expandable system to prolong gastric retention time (GRT):

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

Thus, gastro-retentivity is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Unfoldable and swellable systems have been investigated and recently tried to develop an effective gastro-retentive drug delivery.

Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like; tetrahedron, ring or planner membrane (4 - label disc or 4 - limbed cross form) of bioerodible polymer compressed within a capsule which extends in the stomach. Swellable systems are also retained in the gastro intestinal tract (GIT) due to their mechanical properties. The swelling is usually resulting from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid. Expandable systems have some drawbacks like problematical storage of much easily hydrolysable, biodegradable polymers, relatively short-lived mechanical shape memory for the unfolding system, most difficult to industrialize and not cost effective. Again, permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion and gastropathy.

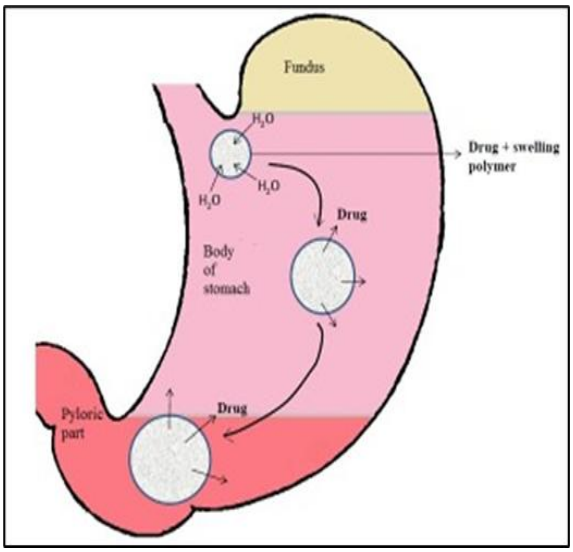


Fig. 5. Expandable drug delivery systems

2.2.6 Application of GRDDS:

- The bioavailability of riboflavin GRDF is significantly enhanced in comparison to the administration of non-GRDF polymeric formulations.
- There are several different processes, related to absorption and transit of the drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption

2.2.6.1 Sustained Drug Delivery/Reduced Frequency of Dosing

- For drugs with relatively short biological half-life, sustained and slow input from GRDF may result in improved pharmacokinetics and reduced dosing frequency.
- This feature is associated with improved patient compliance and thereby improves therapy.

2.2.6.2 Targeted Therapy for Local Ailments in the Upper GIT

- The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine.
- By this mode of administration, therapeutic drug concentrations may be attained locally while systemic concentrations, following drug absorption and distribution, are minimal.

2.2.6.3 Reduced Fluctuations of Drug Concentration

- Continuous input of the drug following GRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms.
- Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented.
- This feature is of special importance for drugs with a narrow therapeutic index.

2.3. Diabetes mellitus:

Diabetes mellitus (DM) is apparently one of the oldest diseases known to man. Diabetes mellitus is a metabolic disease commonly characterised by an elevation of the blood glucose levels that warrant frequent monitoring and proper control. Pancreatic beta cells (β-cells) produce the hormone insulin which facilitates the absorption of glucose into the cells in order to provide energy and is also involved in a variety of other functions. Diabetes mellitus occurs due to lack of insulin production or insulin sensitivity. It is mainly classified into many types, however, the most common types are type 1 and type 2 diabetes mellitus.

Type 1 Diabetes mellitus (T1DM) is typically associated with failure in insulin production resulting from the destruction of pancreatic β-cells by T-cell-mediated autoimmunity. On the other hand, **type 2** Diabetes mellitus (T2DM) is characterised by insulin resistance and reduction of insulin production. Lower life expectancy was found in T1DM compared to T2DM due to the relatively higher incidence of cardiovascular diseases and acute metabolic disorders in the former group. It is important that all forms of diabetes to be diagnosed and managed at the early stage to prevent or slow down its potential complications involving other organs such as diabetic nephropathy, retinopathy, neuropathy, cardiovascular diseases and diabetic foot ulcer.

Diabetes mellitus is a chronic metabolic disorder which is characterized by hyperglycaemia (increased blood sugar level). Diabetes mellitus is caused by imbalanced carbohydrate metabolism and its impacts on other pathways. According to the WHO, diabetes affects 285 million adult patients in 2010, 67% higher than in 2000 and an estimated 439 million in 2030 is 20% higher than the estimated 2030 study. The classification of diabetes has been presented in Table-2.

| Type-1 (IDDM) | Type-2 (NIDDM) |
|---|---|
| Insulin dependent diabetes mellitus | Non-insulin dependent diabetes mellitus |
| Juvenile onset diabetes mellitus | Adult onset diabetes mellitus |
| Occurs in children | Occurs in adults |
| Pancreatic β-cells are destroyed | Less insulin secretion or insulin resistance |
| No insulin secretion | (cells don't respond to insulin) |
| Treatment: insulin injection | Treatment: oral hypoglycaemic agents |

Table-2: Classification of diabetes mellitus

The common symptoms are polydipsia (excess thirst), polyphagia (excess hunger), and polyuria (excess urination).

2.3.1. ANTIDIABETIC AGENTS:

Agents which are used in the treatment of diabetes are called as antidiabetic agents. They used to lower the blood sugar level in patients suffering from hyperglycaemia. These are also called as anti-hyperglycaemic agents.

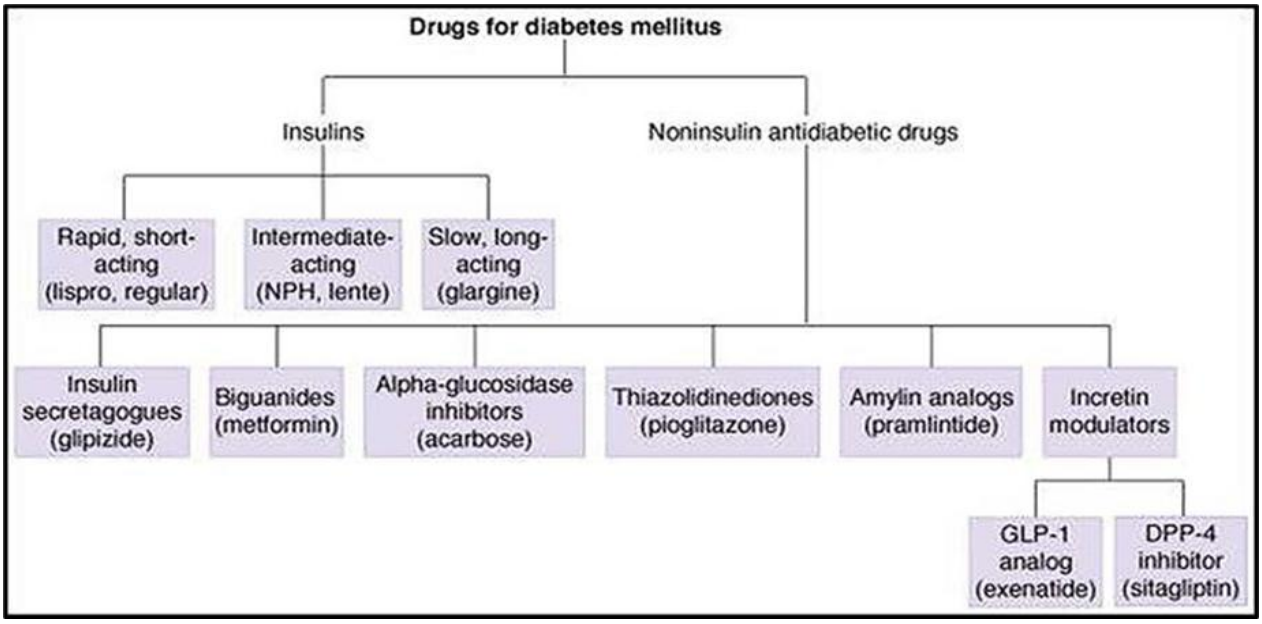


Table 3: Classification of antidiabetic agents

## III. PRESENT STATUS OF GRDDS FOR ANTIDIABETIC DRUGS

Oral therapy is considered as the best path for administration of antidiabetic drugs owing to the highest patient compliance among other routes except insulin which is given as subcutaneous injection, owing to its degradation in GIT. Conventional drug delivery systems or modified drug release systems are the most commonly utilized drug delivery systems. Modified release drug delivery systems are employed to obtain better therapeutic results, this concept is also

applicable to the anti-diabetic drugs. The modified release drug delivery systems that has gained interest in the last decade is gastroretentive drug delivery.

Drugs like metformin hydrochloride which has potential absorption from stomach when given as Controlled Release/Sustained Release dosage form pass through the stomach (absorption region) at faster rate than its release and most of the drug is release in colon where the drug is poorly absorbed. Metformin hydrochloride should therefore be a given in gastro-retentive form while given as controlled release formulation for better efficacy, as gastro-retentive dosage form release the drug slowly for longer periods in the stomach for steady absorption in the intestines.

3.1. Floating drug delivery systems (FDDS):

Patel et al. developed floating Metformin hydrochloride microspheres by nonaqueous emulsifying technique utilizing ethylcellulose as polymer to control drug release. Developed formulations were assessed for pharmacopoeial as well as non-pharmacopoeial tests including drug-polymer compatibility by FTIR, percentage yield, drug entrapment efficiency, particle size determination, surface topography, in-vitro floatation and drug release studies. The results showed that the yields of the developed floating microsphere metformin hydrochloride were 58 - 87% and drug release from microsphere was 47 - 87% after 8 hours and the floating time of > 8 hrs. For the prolonged drug release in the stomach, thereby enhancing bioavailability and patient compliance. [1]

Encapsulated floating Repaglinide microspheres were designed and developed by Sharma et al. to improve the residence time of the drug in GIT and thereby improve its systemic availability. The emulsion solvent diffusion techniques were used to formulate floating microspheres of repaglinide with ethylcellulose (EC) and methylcellulose hydroxypropyl (HPMC) (5 and 100 cps). The floating capacity and in-vivo antidiabetic activity of microspheres was carried out in alloxane-induced diabetic rats. The optimized formulation remained buoyant for six hours and showed marked reduction in blood glucose in comparison to the group of pure drugs. [2]

Kamila et al. prepared floating Rosiglitazone microspheres using non-aqueous emulsification/solvent evaporation techniques by encapsulation of medicine into Edragit RS-100. To attain predetermined target release, simplex lattice mixture layout was used. In-vivo formulation efficiency in streptozotocin-induced diabetic rats has been assessed, optimized formulations (microspheres) of rosiglitazone started to decrease blood glucose in the third hour until the ninth hour until blood glucose reached a standard level while in the case of pure medication the blood glucose declined from second hour to 5 hours. [3]

In combination with the gums (sodium alginate, sodium CMC, xanthan gum and guar Gum) Thulluru et al. developed effervescent floating Pioglitazone tablets with synthetic polymer HPMC K100 M that can extend the release of drug up to 12 hours. Studies of in-vitro buoyancy have shown that the optimized formulation remains buoyant for 12 hours and in-vitro drug release was found to be almost complete in the same time. In-vivo studies of rabbit x-ray imaging showed that the formulation is capable to withstand repeated gastric contractions and remain intact in the gastric region for 12 hours. [4]

Ahmed et al. developed gastro-retentive tablets of Sitagliptin tablets based on floating, the tablets were prepared using the polymers HPMC K100, Poly vinyl pyrrolidine and polyacrylic acid in different concentrations by direct compression method. The bulk mixture was characterized for flow properties and finished formulations were evaluated for pharmacopoeial tests. In-vitro dissolution in the stimulated gastric pH 1.2 and intestinal fluid pH 6.8 were carried and drug releases for optimized formulation were found to be between 92.9-99.28%. The study concluded that good release was observed when a combination of polymers was used instead of single polymer and necessity of combining different class of polymers to get the desirable pharmacokinetic profile. [5]

Jeganath et al. developed a non-effervescent gastro-retentive tablets of Linagliptin (dipeptidyl peptidase-4 enzyme inhibitor) based on floating. The tablets were prepared using a combination of Hydroxy Propyl Methyl Cellulose-K15, Hydroxy Propyl Methyl Cellulose-E15 and chitosan as polymers and Accurel,

Gelucire as low-density drug carriers. The tablets were successfully prepared by direct compression method. The developed formulations remain floating for more than 20 hours in 900ml of simulated gastric fluid pH 1.2 and in-vitro drug release was found to be 98% in 20 hours for the optimized formulation. [6]

**Duggi et al.** developed Pioglitazone hydrochloride floating matrix tablets for gastro-retention using a combination of polymers viz. hydroxy propyl methyl cellulose, xanthan gum and guar gum. The authors studied the effect of polymer concentration and viscosity on gastro-retention and drug release. Based on various combinations they developed the optimized formulation which started floating in 28 seconds and remain floated for more than 12 hours. The optimized formulation has swelling index of 91.8% and drug release up to 95.86% after 12 hours was attained. The authors concluded that floating, swelling and subsequent drug release is highly dependent on polymer concentration and its viscosity. [7]

3.2. Expandable Systems:

Boldhane et al. manufactured effervescent based floating and swelling gastro-retentive tablets of Metformin hydrochloride using sodium alginate as a gelling agent, sodium CMC as release modifier and polymer Eudragit NE 30D as release retardant respectively. The authors used 32 full factorial design to study the effect of concentration of sodium alginate and sodium CMC on release of drug, they selected time required for 50%, time required for 90% of cumulative drug release, Flag and f2 as 4 dependent variable. The statistical model was employed to make the optimization process very effective and quick. The authors also concluded that Low floating time and higher % swelling of the formulation are essential to increase its residence time in the stomach, thereby improving the bioavailability of the drug. [8]

3.3. Mucoahesive drug delivery systems:

Awasthi et al. developed hollow floating Gliclazide beads using a simple ionotropic gelation technique using a combination of low methoxyl pectin and hydroxypropylmethyl cellulose. Particle size analysis of beads revealed the size of dry beads in the range of 730-890µm based on the composition of polymer and concentration of calcium carbonate. The authors also concluded that the mean diameter of beads increases with increase in the concentration of gas forming agent which may be attributed to the increased viscosity of solution. The authors used Fourier transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC) and X-ray diffraction technique to confirm the drug's stable character. Formulations were assessed for mucoadhesion using goat stomach mucosal membrane. The optimized formulations showed excellent bioadhesive properties for a duration of 2h in the mucoadhesion experiment. The in-vitro drug release represents Fickian diffusion with swelling. Glipizide microspheres were also developed by Patel et al. through simple emulsification phase separation method using chitosan as polymer for mucoadhesion and glutaraldehyde as a cross-linking agent. A full factorial 32 design was used using two independent variables (polymer-to-drug ratio and stirring speed) and four dependent variables (percentage mucoadhesion, $t_{80}$, drug entrapment efficiency). The best exhibited formulation showed entrapment effectiveness of 75%, a swelling index of 1.42, a mucoadhesion of 78% after one hour and the drug release also maintained up to 12 hours. The in vivo research in Wistar mice also reveals an important hypoglycemic impact up to 12 hours. [9]

Prasanthi et al. developed mucoadhesive microspheres of Linagliptin by ionotropic gelation and single emulsion methods using synthetic polymers like carbopol 934P, guar gum, HPMC K100M and sodium carboxy methyl cellulose. Spherical free flowing microspheres of linagliptin were successfully prepared by emulsification method. The developed mucoadhesive microspheres has swelling index of 1.03, entrapment efficiency of 85±0.57% and the mean particle size of 135±6µm. Mucoadhesion strength was found to be 87% in 7 hrs. and drug release was shown to be 98.2±0.63% in 8 hrs. and release kinetics followed anomalous transport mechanism. Radiographic studies were performed in rabbits and microspheres retained for 7 h in the rabbit stomach as confirmed by the images. [10]

Sarkar et al. developed poly (acrylic acid)-grafted-gellan-based gastroretentive continuous release tablets of Metformin hydrochloride based on swelling and mucoadhesion. Firstly authors synthesized poly (acrylic acid)-grafted-gellan by microwave-promoted cerric (IV) ion initiated graft copolymerization

technique. The yield of polymer was found to be dependent on concentration of cerric (IV) ammonium nitrate and acrylic acid. Further they developed mucoadhesive sustained release tablet using metformin hydrochloride as drug by wet granulation. The formulations developed showed sustained release potential in simulated gastric fluid (pH 1.2) over a period of 10 hours. [11]

3.4. Dual (floating) and bioadhesive systems:

Sah et al. developed floating Sitagliptin microsphere applying 32 factorial design to improve the gastric residence time and subsequent absorption of the drug in the stomach. The authors prepared microspheres using HPMC K4M and psyllium husk as swelling agents by ionotropic gelation method. In X-ray imaging in rabbits initially and after 24 hours of administration of dosage form, microspheres were found retained in the stomach. During in-vivo study sitagliptin was detected in plasma from swellable gastroretentive microsphere till the end of 24 hours post-administration, while the plasma concentration of conventional microsphere of sitagliptin was detectable till 12 hours post administration. The swelling of the developed formulation was found to be 191% to 240% and for the optimized formulation, in-vitro release of drugs was found to be 99.2% after 24 hours. [12]

3.5. In-Situ Gelling systems (Raft Forming system):

Another method of gastroretention with excellent patient compliance is the in-situ gelling systems (also known as the raft forming system figure 6). These structures comprise of sodium alginate as polymer-forming gel in-situ with carbonate or bicarbonates as effervescent substances. These systems are in the solution form initially but when they come in contact the gastric fluid, they get swell to form viscous cohesive gel and generate carbon dioxide bubbles these bubbles are caught in the gel which cause drug delivery systems to float. Raft forming systems are used mostly for gastroesophageal treatment because they are likely to produce a layer on top of the gastric fluid.

It were developed by Senjoti et al. Box-Behnken experimental design was used to develop tablets with effervescent and swelling properties using a combination of sodium bicarbonate and HPMC-PEO (Poly Ethylene Oxide) polymer. The developed tablets were able to float within 4 minutes, remain in floating condition for 24 h and sustained the release of drug for 12 hours. Metformin hydrochloride floating gastro-retentive tablets of based on in-situ gel technique. The authors also concluded that amount of polymer matrix (amount of HPMC and PEO), effervescent agent (sodium bicarbontate), and swelling enhancer (SSG) affected and floating and drug release from the formulation. [13]

In-situ miglitide formulations, using gellan gum and sodium alginate as gelling agent, propylene glycol as co-solvent and calcium carbonate were developed by Mahmoud et al. Calcium carbonate dissociates in the acidic environment to release carbon dioxide which gets entrapped in the gel and helps in the floating. Developed formulations showed reasonable viscosity and formed a firm gel that floated over the surface in seconds and remained floating for 24 hours when it came into contact with simulated gastric fluid. In-vitro dissolution was achieved at 900 mL 0.1N HCl (pH 1.2), and the release of all formulations exceeds 70% in 24 hours. The in-vivo pharmacokinetic experiments were performed in 10 New Zealand rabbits and the results reveal 1.79 fold increase in Cmax and 18.4 fold increase in AUC with the newly developed in-situ formulation compared to the one on the market. The authors concluded that use of propylene glycol in the formulation helped in solubilization the water insoluble drug. [14]

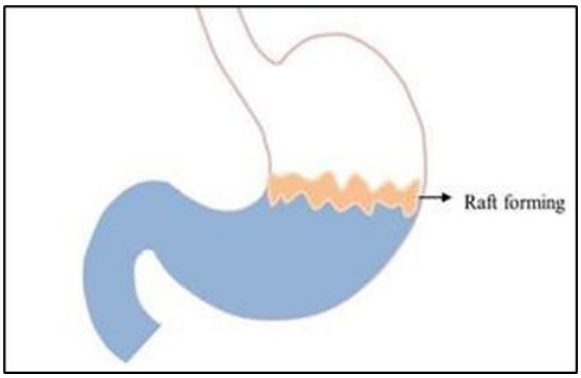


Fig. 6. In-Situ Gelling systems (Raft Forming system)

3.6. Superporous Hydrogels:

Superporous hydrogel (figure 7) is characterized by a three-dimensional network of hydrophilic polymer, which absorbs a huge amount of water in a short period of time, due to the presence of interconnected

microscopic pores. These highly swollen hydrogels remain in the stomach for a long period of time when used as drug carriers, releasing virtually all loaded drugs, large volumes and sheer bulk of these hydrogels does not allow them to be transported through the pylorus to the next organ. This distinct swelling characteristic enables them to be used as gastro-retentive carriers that provide a sustained release through extended gastric retention. Not only are hydrogels needed to swell rapidly, but they should also be biocompatible, biodegradable, better swelling properties, strong mechanical strength and remain static in acidic situation

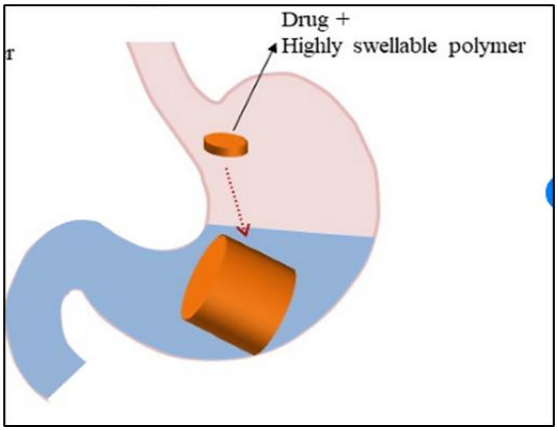


Fig. 7. Superporous Hydrogels

Park et al. developed hydrogels of chitosan-glycol and chitosan by a gas blowing method and studied their swelling behaviours in acidic solution to explore their use as a stomach retention dosage form. Firstly the stock solution of chitosan and glycol-chitosan were prepared dissolving the former in 0.01M acetic acid and latter in water respectively. The pH of the solution was adjusted to 5 by adding acetic acid, then sodium bicarbonate (blowing agent) is added to the solution and mixed vigorously by stirring for 30seconds. Foaming started immediately and completed in 2 minutes. The formed hydrogels were stored at room temperature and freeze dried before use. Both the chitosan and glycol chitosan hydrogels revealed higher swelling ratio in acidic environment than in distilled water probably due to the cationization of amine groups in acidic environment. The results also indicated that swelling of hydrogels with increasing density of crosslinking agent. [15]

Gupta et al. formulated chitosan/polyvinyl alcohol) interpenetrating polymer-type superporous hydrogels of Rosiglitazone maleate utilizing glyoxal as crosslinker. To induce the porous structure, sodium bicarbonate was used as a foaming agent. The swelling of the formulation depended on the amount of chitosan and crosslinker. The drug release from the superporous hydrogels was maintained for 6 hours successfully. [16]

3.7. Magnetic Systems:

These devices contain a tiny inner magnet in the design and an external magnet is positioned on the abdomen above the stomach location. Gastro retention of the dosage form can be improved by applying an extracorporeal magnet for localization to a specific part. The site of magnet should be designated with very high precision to acquire the desired results in such systems. Thus, the factual significance of such systems is frequently doubtful.

Angelopoulou et al. developed magnetically targetable nanocarriers of the sodium-glucose transporter protein (SGLT2) inhibitor dapagliflozin for the selective delivery of dapagliflozin in tumors. The dapagliflozin-loaded PMMA-g-PEGMA nanoparticles showed concentration-dependent toxicity against the A549 cancer cell line. The application of an external magnetic magnet increases the uptake of nanoparticles by cells, leading to increased cytotoxicity. The developed nanoparticles exhibited satisfactory drug loading efficiency and high colloidal stability. Dapagliflozin release from the nanoparticles responded to an AC magnetic field to induce dapaglifozin release in close proximity to the tumor area confirming accumulation of the dapaglifozin-loaded nanoparticles at the tumor cells due to magnetic targeting. [17]

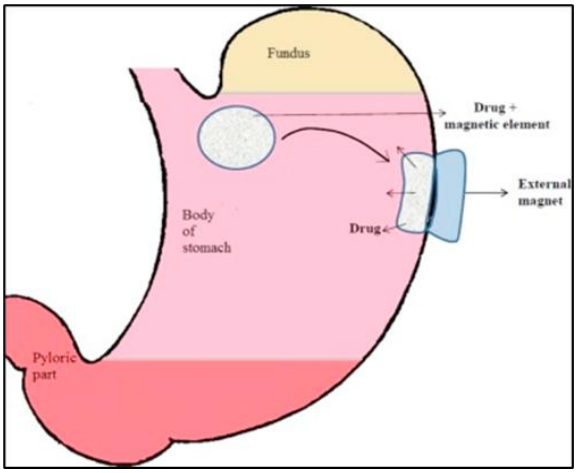


Fig. 8. Magnetic Systems

## IV. CHALLENGES AHEAD WITH GRDDS

The retention time of the dosage forms in the GIT is one of the determinants of the bioavailability of oral drug delivery systems. In case of GRDDS, it is rather specific to the stomach only. Therefore, for developing a GRDDS, the main challenge is retaining the delivery system in the stomach or the upper part of the small intestine for a long time until all the drugs have been released at a predetermined rate. The process of gastric emptying time is highly variable. Among many other factors, it mainly depends on the dosage form as well as fed or fasted state of the stomach. The gastric retention time is extended in the fed state, whereas shortened by the fasting state. Other physiological barriers and factors like the type of food, caloric content, gender and age play significant roles in the variation of gastric emptying time. Because of high caloric content, high fat meal strongly prolongs the process of gastric emptying. Indigestible polymers or fatty acid salts also modify the motility pattern of the stomach under fed state and help in reducing gastric emptying rate. Additionally, patients have variable GRT depending on gender and age. The pylorus limitation plays an important role in gastric retention of any GRDDS. The pylorus size is about 2 to 3 mm during the digestion and the diameter becomes $12.8 \pm 7.0$ mm during the inter-digestive phase. Thus, all particles must have a diameter lower than 5 mm so that they can pass through the pylorus into the duodenum. Another factor to consider here is the variation in pylorus size and its peristaltic movement of the animal (e.g. dog, rabbit model) from that of the human.

So, in vivo efficacy results need to be concluded carefully.

Size and shape of the dosage form, individual's disease state, and body mass index are some other factors on which gastric residence time is dependent and related to the efficacy of the dosage form. However, it has been reported that sometimes multiple-unit GRDDS shows an improved and predictable drug release compared to a single-unit GRDDS. Due to a combination of the lag time and the gastric emptying process, a single unit gastro-retentive dosage form (GRDF) may ultimately exit the stomach before the dosage form becomes functional. Hence, to develop an optimum GRDDS, the main challenges are to overcome the problems associated with the gastric emptying rate of the stomach together with maintaining an appropriate drug release rate for an extended period of time before it gets metabolized in the system. [19]

## V. CONCLUSION

Gastro-retentive drug delivery systems are successfully developed and reported for antidiabetic drugs by researchers and they can do wonders if the same are available commercially. These systems are very useful for the drugs which are absorbed from the stomach. Further investigation in human volunteers still needs to done before scaling up them in to commercials. The formulation work is still in progress to develop the gastro-retentive dosage form of these drugs which can be commercialized. With increasing population of diabetics there is further scope of development in this field for the economical products with better therapeutic results and reduced side effects especially for prolonged use.

Although several approaches like floating, bio-adhesion, effervescence, sinking, magnetic, swelling, etc. have been proposed over the years, reports on their *in vivo* success have not been captured significantly. Formulation wise, the major trend has been shifted toward the use of swelling polymer matrix together with effervescence in the design of floating delivery systems. Commercially it is emerging slowly as an important novel drug delivery due to many inherent challenges associated with it in spite of the numerous potential benefits offered by this delivery system. In terms of delivering drugs to the systemic circulation along with enhanced effectiveness, it is expected that GRDDS will become more popular in the near future. However, it is necessary to establish their efficacy by properly designed *in vivo* studies for a specific drug because of the complexity in pharmacokinetic and pharmacodynamic parameters. [19]

## REFERENCE

[1] Patel AS, Roy SS, Thakur RS. Invitro evaluation and optimization of controlled release Floating Drug Delivery System of metformin hydrochloride. DARU-Journal of faculty of pharmacy. 2006;14, page no.257–264.

[2] Sharma M, Kohli S, Dinda A. In-vitro and in-vivo evaluation of repaglinide loaded floating

microspheres prepared from different viscosity grades of HPMC polymer. Saudi Pharmaceutical Journal. 2015;23(6),page no.675–682.

[3] Kamila MM, Mondal NK, Ghosh LK, Gupta Bundefined. Multiunit Floating Drug Delivery System of Rosiglitazone Maleate: Development, Characterization, Statistical Optimization of Drug Release and In Vivo Evaluation. AAPS PharmSciTech. 2009;10(3): page no.887–899

[4] Thulluru A, Varma MM, Setty CM, Anusha A, Chamundeeswari P, Sanufar S. Formulation, in vitro and in vivo evaluation of pioglitazone hydrochloride - Effervescent gastro retentive floating hydrophilic matrix tablets. International Journal of PharmTech Research. 2016;9(7):page no.388–398.

[5] Ahmed MG, Sanjana A, Rajeev V. Design and optimization of gastroretentive drug delivery system of sitagliptin. International Journal of Pharmaceutical Sciences and Research. 7(5):Page no.2187–2193.

[6] Jeganath S, Shafiq KM, Mahesh PG, S SK. Formulation and evaluation of non-effervescent floating tablets of linagliptin using low-density carriers. Drug Invention Today. 2018;10(3):page no.322–329.

[7] Duggi S, Narendra Chary T . Studies on formulation development of gastroretentive drug delivery system for pioglitazone hydrochloride. International Journal of Pharmacy. 2014;4(3): page no.241–254 .

[8] Boldhane S, Kuchekar B. Gastroretentive Drug Delivery of Metformin Hydrochloride: Formulation and In Vitro Evaluation Using 32 Full Factorial Design. Current Drug Delivery. 2009;6(5):page no.477–485.

[9] Awasthi R, Kulkarni GT. Development of Novel Gastroretentive Floating Particulate Drug Delivery System of Gliclazide. Current Drug Delivery. 2012;9(5):page no.437-451

[10] D P, Yanmanagandla D, Sripada RD. Formulation and Evaluation Of Linagliptin Mucoadhesive Microspheres. International Research Journal Of Pharmacy. 2018;9(5):page no.11–7.

[11] Sarkar D, Nandi G, Changder A, Hudati P, Sarkar S, Ghosh LK. Sustained release gastroretentive tablet of metformin hydrochloride based on poly (acrylic acid)-grafted-gellan. International Journal of Biological Macromolecules. 2017;96:page no.137–148.

[12] Sah SK, Tiwari A, Shrivastava B. Formulation Optimization and In-Vivo evaluation of Floating Gastroretentive Microsphere of Sitagliptin by 32 Factorial Design. International Journal of Pharmaceutical Sciences Review and Research. 2016;40(2):page no.198–206.

[13] Senjoti FG, Mahmood S, Jaffri JM, Mandal UK. Design and In-vitro Evaluation of Sustained Release Floating Tablets of Metformin HCl Based on Effervescence and Swelling. Iranian Journal of Pharmaceutical Research. 2016;15(1):page no.53–70.

[14] Mahmoud DB, Shukr MH, Elmeshad AN. Gastroretentive Cosolvent-Based In Situ Gel as a Promising Approach for Simultaneous Extended Delivery and Enhanced Bioavailability of Mitiglinide Calcium. Journal of Pharmaceutical Sciences. 2019;108(2):page no.897–906.

[15] Park H, Park K, Kim D. Preparation and swelling behavior of chitosan-based superporous hydrogels for gastric retention application. Journal of Biomedical Materials Research Part A. 2006;76A(1):page no.144–50.

[16] Gupta N, Shivakumar H. Preparation and Characterization of Superporous Hydrogels as pH-Sensitive Drug Delivery System for Pantoprazole Sodium. Current Drug Delivery. 2009;6(5):page no.505–10.

[17] Angelopoulou A, Voulgari E, Kolokithas-Ntoukas A, Bakandritsos A, Avgoustakis K. Magnetic Nanoparticles for the Delivery of Dapagliflozin to Hypoxic Tumors: Physicochemical Characterization and Cell Studies. AAPS PharmSciTech. 2017;19(2):page no.621–33.

[18] A Review of Gastro-retentive Drug Delivery Systems for Antidiabetics and its present status. 10.5958/0974360X.2021.00098.6.Aseem Kumar*, Anil Kumar Sharma, Rohit Dutt, School of Medical and Allied Sciences (SoMAS), G. D. Goenka University, Sohna Road, Gurugram, Haryana, India.

[19] Asian Journal of Pharmaceutical SciencesVolume 11, Issue 5, October 2016, Pages 575-584 Review on Gastro-retentive drug delivery systems and their *in vivo* success: A recent updateAuthor links open

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[22] M.S. Wong *et al.*Gene therapy in diabetesSelf Nonself(2010)
[23] 1. Schneider F, Koziolek M, Weitschies W. In vitro and in vivo test methods for the evaluation of gastroretentive dosage forms. *Pharmaceutics.* 2019; page no.411-416.
[24] Boulton DW, Fawcett JP. Enantioselective disposition of albuterol in humans. *Clin Rev Allergy Immunol.* 1996;14: page no.115–138.
[25] Chandira RM, Palanisamy P, Jaykar B. Formulation and evaluation of bilayered floating tablets of metformin hydrochloride. *Int Res J Pharm.* 2012;3: page no.257–267.
[26] Menon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. *J Pharm Sci.* 1994;83: page no.239–245.
[27] Levy G, Jusko WJ. Factors affecting the absorption of riboflavin in man. *J Pharm Sci.* 1966;55: page no.285–289.
[28] Badoni A, Ojha A, Gnanarajan G, Kothiyal P. Review on gastroretentive drug delivery system. *J Pharm Innov.* 2012;1: page no.32–42
[29] Malpure PS, Chavan BR, Maru AD, Bhadhane JS, Thakare EB, Sonawane PS. Gastroretentive drug delivery systems. *World J Pharm Pharm Sci.* 2019;8: page no.506–528.
[30] Schneider F, Koziolek M, Weitschies W. In vitro and in vivo test methods for the evaluation of gastroretentive dosage forms. *Pharmaceutics.* 2019; page no.411:416.
[31] Boulton DW, Fawcett JP. Enantioselective disposition of albuterol in humans. *Clin Rev Allergy Immunol.* 1996;14: page no.115–138..
[32] Chandira RM, Palanisamy P, Jaykar B. Formulation and evaluation of bilayered floating tablets of metformin hydrochloride. *Int Res J Pharm.* 2012;3: page no.257–267.
[33] Menon A, Ritschel WA, Sakr A. Development and evaluation of a monolithic floating dosage form for furosemide. *J Pharm Sci.* 1994;83: page no.239–245.
[34] Levy G, Jusko WJ. Factors affecting the absorption of riboflavin in man. *J Pharm Sci.* 1966;55: page no.285–289.
[35] Badoni A, Ojha A, Gnanarajan G, Kothiyal P. Review on gastroretentive drug delivery system. J Pharm Innov. 2012;1: page no.32–42.
[36] Malpure PS, Chavan BR, Maru AD, Bhadhane JS, Thakare EB, Sonawane PS. Gastroretentive drug delivery systems. World J Pharm Pharm Sci. 2019;8: page no.506–528.
[37] More S, Gavali K, Doke O, Kasgawadek P. Gastroretentive drug delivery system. J Drug Deliv Ther. 2018;8: page no.24–35.
[38] Tomar A, Upadhyay A, Gupta S, Kumar S. An overview on gastroretentive drug delivery system: current approaches and advancements. Res Pharm Sci. 2019;9: page no.12–16.
[39] Taylor K, Aulton M. Aulton's Pharmaceutics. The design and manufacture of medicines (4th ed) Churchill Livingstone; London. 2007; page no.397.
[40] Gandhi A, Verma S, Imam SS, Vyas M. A review on techniques for grafting of natural polymers and their applications. Plant Arch. 2019;19: page no.972–978.
[41] Chudiwal V, Shahi S, Chudiwal S, Ahale D. Innovative technologies for gastro-retentive. Asian J Pharm Res. 2017;6: page no.22–28.
[42] Devkant S, Anjali S. Gastro retentive drug delivery system. A review. Asian Pac J Health Sci. 2014;1: page no.80–89.
[43] Clarke GM, Newton JM, Short MB. Comparative gastrointestinal transit of pellet systems of varying density. Int J Pharm. 1995;114: page no.1–11.
[44] Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery system. Expert Opin Drug Deliv. 2006;3: page no.217–233.
[45] Garg R, Gupta GD. Progress in controlled gastroretentive delivery systems. Trop J Pharm Res. 2008;7: page no.1055–1066.

[46] Thapa P, Jeong SH. Effects of formulation and process variables on gastroretentive floating tablets with a high-dose soluble drug and experimental design approach. Pharmaceutics. 2018;10: page no.161

[47] Patel A, Modasiya M, Shah D, Patel V. Development and in vivo floating behavior of verapamil HCl intragastric floating tablets. AAPS PharmSciTech. 2009;10: page no.310–315

[48] Nayak AK, Maji R, Das B. Gastroretentive drug delivery systems: a review. Asian J Pharm Clin Res. 2010;3: page no.2–10.

[49] Nasa P, Mahant S, Sharma D. Floating systems: a novel approach towards gastro retentive drug delivery systems. Int J Pharm Pharm Sci. 2010;2: page no.2–7

[50] Zhao Z, Wu C, Zhao Y, Hao Y, Liu Y, Zhao W. Development of an oral push-pull osmotic pump of fenofibrate-loaded mesoporous silica nanoparticles. Int J Nanomedicine. 2015; 10:1691–1701. Erratum in: Int J Nanomedicine. 2022;17: page no.15-16.

[51] Saisivam S, Ulla MR, Shakeel F. Development of floating matrix tablet of losartan potassium: in vitro and in vivo evaluation. J Drug Deliv Sci Technol. 2013;23: page no.611–617.

[52] Moursy NM, Afifi NN, Ghorab DM, El-Saharty Y. Formulation and evaluation of sustained release floating capsules of nicardipine hydrochloride. Pharmazie. 2003;58: page no.38–43.

[53] Samal HB, Dey S, Kumar D, Kumar DS, Sreenivas SA, Rahul V. Formulation, characterization and in-vitro evaluation of floating microspheres of nateglinide. Int J Pharm Bio Sci. 2011;2: page no.147–157.

[54] Pal P, Sharma V, Singh L. A review on floating type gastroretentive drug delivery system. Int Res J Pharm. 2012;3: page no.37–43.

[55] Meka L, Kesavan B, Chinnala KM, Vobalaboina V, Yamsani MR. Preparation of a matrix type multiple-unit gastro retentive floating drug delivery system for captopril based on gas formation technique: in vitro evaluation. AAPS PharmSciTech. 2008;9: page no.612–619.

[56] Verma R, Kumar A, Purohit S, Bhandari A. Overview of gastro-retentive drug delivery system. J Natura Conscientia. 2011;2: page no.423–436

[57] Atyabi F, Sharma HL, Mohammad HAH, Fell JT. In vivo evaluation of novel gastric retentive formulation based on ion exchange resin. J Control Release. 1996;42: page no.105–113.

[58] Ali A, Shahid MA, Hossain MD, Islam MN. Antibacterial bi-layered polyvinyl alcohol (PVA)-chitosan blend nanofibrous mat loaded with Azadirachta indica (neem) extract. *Int J Biol Macromol.* 2019;138: page no.13–20.

[59] Nayak AK, Malakar J. Formulation and in vitro evaluation of hydrodynamically balanced system for theophylline delivery. *J Basic Clin Pharm.* 2011;2: page no.133–137. .

[60] Gupta P, Kumar M, Kaushik D. Pantoprazole sodium loaded microballoons for the systemic approach: in vitro and in vivo evaluation. *Adv Pharm Bull.* 2017;7: page no.461–467.