IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
**Review Article**
December 2016 Vol.:8, Issue:1


# A New Venture in Drug Delivery: Bilayer Floating Tablet of Loop Diuretics with Potassium Supplement: A Review

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**Submission:** 5 December 2016
**Accepted:** 10 December 2016
**Published:** 25 December 2016



**Keywords:** Loop diuretics, potassium chloride, hypertension, bilayer floating tablet, Diumide-K Continus Tablets

**ABSTRACT**

Loop diuretics are diuretics that act at the ascending limb of the loop of Henle in the kidney. They are primarily used in medicine to treat hypertension and edema often due to congestive heart failure or insufficiency. While thiazide diuretics are more effective in patients with normal kidney function, loop diuretics are more effective in patients with impaired kidney function. Diumide-K Continus Tablets contain the diuretic furosemide and potassium chloride. Furosemide is a loop diuretic, inhibiting resorption from the ascending loop of Henlé. It is used for the treatment of oedematous states of various aetiologies. Potassium chloride is present in the tablets to counteract the urinary loss of potassium induced by furosemide.The furosemide layer has normal release characteristics. Furosemide produces a diuresis within one hour and it is complete within six hours. Furosemide has a biphasic half-life in the plasma with a terminal elimination phase of up to about 11/2 hours. Oral route is most often route for administration of drug. Tablet is the most convenient oral dosage form and preferred by patient and physicians. Bilayer floating tablet is suitable for sequential release of two drugs in combination in which one layer is sustained release and another layer is an immediate release. Floating drug delivery systems are one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. Anti-hypertensive and diuretic frequently coexist and may require concomitant drug treatment in heart failure. The potassium chloride in Diumide-K Continus Tablets is incorporated in the controlled release system. This ensures a prolonged release giving maximum absorption and avoiding 'flushing out' of the potassium by the action of the diuretic.

## INTRODUCTION [1-3]

Loop diuretics are the most effective and commonly prescribed drugs in heart failure and are usually given with potassium supplements because of the risk of hypokalemia. However, a review of the literature suggested that, contrary to general opinion, the fall in serum potassium, and thus the frequency of hypokalemia, was much less with the loop diuretics than with the thiazides (Morgan & Davidson, 1980). Nevertheless, a number of preparations have been developed where a loop diuretic is combined with either a potassium supplement or a potassium-sparing diuretic. We have compared the effect of two diuretics and diuretic/potassium combinations on plasma and red cell electrolytes in patients with stable heart failure. Frusemide and bumetanide were given without supplements and as combination therapy, Diumide K (frusemide 40 mg, potassium 8 mmol) and Burinex K (bumetanide 0.5 mg, potassium 7.7 mmol) per tablet in an open crossover study. Loop diuretics—one type of diuretic or "water pill" named after the part of the kidney it acts on—are commonly used in the treatment of heart failure (and associated lower-limb edema or swelling) to help push out extra fluid that can accumulate when the heart is not working properly. But they also flush out needed potassium, causing many doctors, but not all, to prescribe the supplements. Only patients receiving supplemental potassium in solid, not liquid form, were studied, the latter possibly being indicative of an inability to swallow and therefore a marker for a possibly complicating corollary medical impairment. Loop diuretics act at the ascending loop of Henle in the kidney and help the body push out extra fluid that could accumulate in the lungs or legs and ankles when the heart is unable to completely pump blood throughout the body. But they may also cause the body to eliminate excessive amounts of potassium, which might be expected to increase mortality from heart arrhythmias. The concept of floating drug delivery system (FDDS) was described in literature as early as1968. Gastric floating drug delivery systems (GFDDS) offer numerous advantages over the gastric retentive systems. These systems have a density lower than the gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the stomach. Floating dosage forms are oral dosage forms of tablets, capsules, or microbeads and contain hydrocolloids that allow floating by swelling thereby prolong the residence time of dosage form GIT. Gastric emptying is a complex process and one of the most important obstacles in the better absorption and enhances bioavailability of oral drug delivery system.

**Stomach Anatomy**[4- 12]

The main function of the stomach is to process and transport food. It serves as a short-term storage reservoir, allowing a rather large meal to be consumed quickly. Vigorous contractions of gastric smooth muscle mix and grind foodstuffs with gastric secretions, resulting in liquefaction of food. As food is liquefied in the stomach, it is slowly released into the small intestine for further processing. Anatomically the stomach is divided into 3 regions: fundus, body, and antrum (pylorus). The proximal part made of fundus and body acts as a reservoir for undigested material, whereas the antrum is the main site for mixing motions and act as a pump for gastric emptying by propelling actions. Gastric emptying occurs during fasting as well as fed states. The pattern of motility, however, distinct in the 2 states. During the fasting state an inter-digestive series, of electrical events take place, which cycles both through stomach and intestine every 2 to 3 hours. This is called the inter-digestive myloelectric cycle or migrating myoelectric cycle (MMC), which is further divided into 4 phases. Anatomy of stomach illustrated in Figure 1.

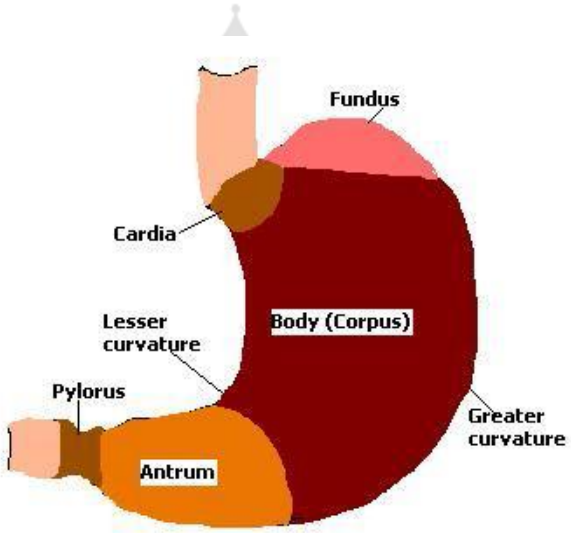



**Figure 1: Anatomy of stomach**

**Ideal Drug Property Of Grdds**[5-7]

Drugs with flowing properties are suitable for GRDDS

1. Drugs acting locally in the stomach, e.g. Antacids and drugs for H. Pylori viz., Misoprostol

2. Drugs that are primarily absorbed in the stomach and upper part of GI, e.g. Amoxicillin, Calcium Supplements, Chlordiazepoxide and Cinnarizine.
3. Drugs that is poorly soluble at alkaline pH, e.g. Furosemide, Diazepam, Verapamil HCL, Chlordiazepoxide etc.
4. Drugs with a narrow window of absorption in GIT, e.g. Riboflavin, Para Aminobenzoic Acid, Cyclosporine, Methotrexate, Levodopa etc.
5. Drugs which are absorbed rapidly from the GI tract. e.g. Metronidazole,tetracycline.
6. Drugs that degrade or unstable in the colon. e.g. Captopril, Ranitidine HCL, Metronidazole, Metformin HCl.
7. Drugs that disturb normal colonic microbes, e.g. Amoxicillin Trihydrate, etc

**Mechanism of Floating System** [5- 9]

While the system is floating on the gastric the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach besides minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to main submerged object. The object floats better if F is on the higher positive side.This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

$$F = F_{buoyancy} - F_{gravity} = (Df - Ds)\, gv \text{ total vertical force,}$$

Where, Df = fluid density, Ds = object density, v = volume and g = acceleration due to gravity.

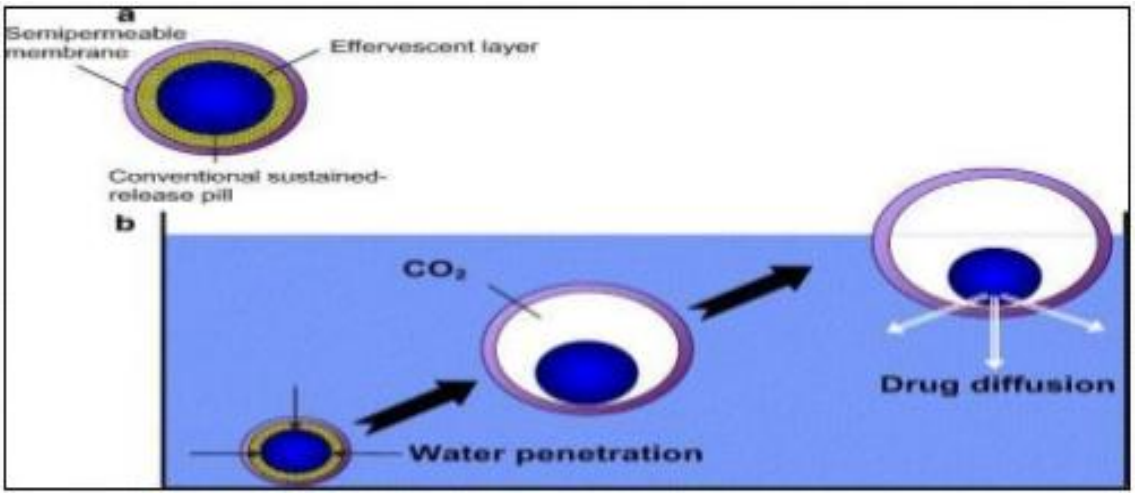



**Figure 2: Mechanism of Floating system**

**Introduction to floating bilayer tablet** [13]

Bilayer tablets contain immediate and sustained release layer. Immediate release layer delivers the initial dose, it contains super disintegrants which increase drug release rate and start onset of action whereas sustained release layer float due to gas generating agent and releases drug at sustained manner for prolonged period. Bilayer tablets are composed of two layers of granulation compressed together. They have appearance of a sandwich because the edges of each layer are exposed. They have the appearance of a sandwich because the edges of each layer are exposed.

**Advantages of Bilayer Floating Tablet**

1. Bilayer floating tablet provide sustained drug delivery like HBS dosage form modify gastric residence time as this system remains in stomach for many hours.
2. It maintains optimum therapeutic window as a result drug delivery with controlled released is achieved.
3. Better patient compliance is achieved due to its ease of administration.
4. It maintains constant blood level.
5. Site-specific drug delivery is achieved for the drugs such as furosemide and riboflavin which are formulated as floating system.
6. Overall other oral routes, these are microbiologically and chemically stable.
7. Due to higher dose precision and lesser content variation, they are the most compatible oral dosage form.

8. They offer the most flexible dosage form.
9. This system is better suited for large scale production.
10. Masking of bitter taste and bad odor by coating can be possible.
11. Swallowing of tablets is easy.
12. Lesser cost as compared to other oral dosage forms.
13. This system is lighter and compact.

**Disadvantages of Bilayer Floating Tablet**

1. This system requires increased fluid levels required in the stomach so that the system floats properly.
2. Drugs with solubility and stability problem in stomach cannot be formulated.
3. Irritation producing drugs on gastric mucosa can be formulated as floating dosage form.
4. Capping is the major problem in bilayer tablets.
5. Separation of layer occurs due to insufficient bonding and reduction in yield occur.
6. Hardness is another problem with bilayer tablet.
7. There may be chances of cross contamination between two layers.
8. Due to low density and amorphous nature of some drugs, compacts do not form because they resist compression.
9. There is less control over weight of individual layer.
10. Swallowing problem in case of children and unconscious patients.
11. Bioavailability problem occurs in case of poor wetting and less dissolution properties.
12. Sometimes encapsulation or coating is required for the drugs that are oxygen sensitive, bitter tasting and with bad odor.

**Techniques of Bilayer Floating Tablet[10- 12]**

1. Oros ® Push-Pull Technology

2. L-Oros Tm Technology

3. DUROS Technology

4. Elan Drug Technologies' Dual Release Drug Delivery System

5. EN SO TROL Technology

6. Rotab Bilayer

7. Geminex Technology.

**1. Oros® Push-Pull Technology**:

Two or three layer system a drug layer and push layer. Drug layer contains drug with other agents and due to this drug is less soluble. Sometimes suspending agent and osmotic agent are also added. The tablet core is surrounded by semi-permeable membrane.

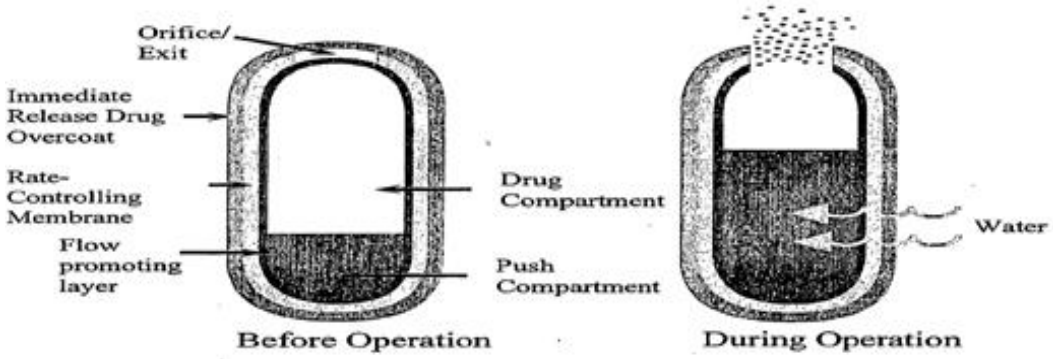



**Figure 3: Oros® Push-Pull Technology**

**2. L-Oros Tm Technology**

Alza developed L-OROS system due to solubility problem. The system contains a drug in dissolved state in a lipid soft gel product which is produced first and then barrier membrane, after which osmotic membrane and semi-permeable membrane coat is applied and is then drilled out through external orifice.

**3. DUROS Technology**

This technology is also known as miniature drug dispensing system which works like a miniature syringe and releases small quantity of drug consistently over a period of time. There is an outer cylindrical titanium alloy reservoir which has high impact strength due to which drug molecules inside it are protected from enzymes.

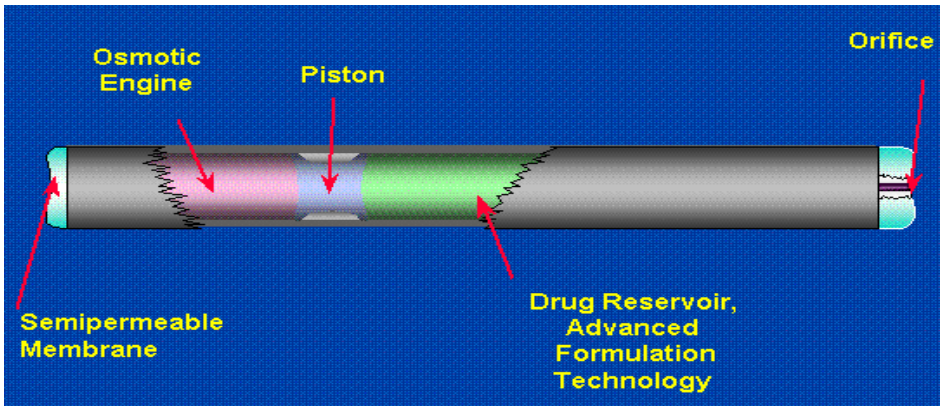



**Figure 4: DUROS Technology**

**4. Elan Drug Technologies' Dual Release Drug Delivery System**

The DUREDASTM Technology provides combination release of drugs together and different release pattern of single drug i.e. it provides sustained release as well as immediate release. This technology provides various advantages i.e. two drug components provide tailored release and it's another benefit is that it consist of bilayered tablet technology in which it contains modified as well as immediate release pattern in one tablet. In this different controlled release, formulations are combined together.

**5. EN SO TROL Technology**

An integrated approach is used by Shire laboratory for drug delivery system which focuses on identification and incorporation of enhancer which is identified to form optimized dosage form in controlled release system. By this enhancement in solubility can be achieved.

**6. RoTab Bilayer**

RoTab bilayer when using is switched to production mode. Dose and compression force is automatically regulated by adjusting filling speed and die table. Hardness is also regulated when required.

**7. Geminex Technology**

In this drug delivery system at different times more than one drug can be delivered. This technology basically increases the therapeutic efficacy of the drug by decreasing its side

effects. It is useful both to industry as well as patient as in single tablet it provides delivery of drug at different rates.

**Characterization of bilayer floating tablets[13].**

*In-vitro* evaluation of floating tablets is performed to assess the physicochemical properties and release characteristics of the developed formulations.

**A) Pre-compression parameters**

**1) Angle of Repose**

In powder, frictional forces can be measured with the help of angle of repose. Angle of repose is the maximum angle which is possible between surface of pile of powder and horizontal plane i.e. height.

$$\tan\Theta = h/r$$

$$\Theta = \tan^{-1} h/r$$

Where Θ = Angle of repose, h= height of pile, r= radius of pile.

**2) Compressibility Index**

The propensity of the powder to be compressed is measured by compressibility index and it also helps in measurement of settling property and interparticulate interaction.

$$\text{Compressibility index (\%)} = \rho t - \rho o * 100 / \rho t$$

Where, ρt = Tapped density gram/ml,

ρo = Bulk density gram/ml.

**3) Bulk Density**

It is denoted by ρb and is defined as mass of powder divided by bulk volume (The United States Pharmacopoeial Convention Stage 6 Harmonization Official December 1, 2012,616.).

**4) Tapped Density**

An increase in bulk density which is attained after mechanical tapping in measuring cylinder is called as tapped density.

**Tapped density= Weight of powder taken/Tapped Volume**

**5) Hausner Ratio**

The propensity of the powder to be compressed is measured by Hausner ratio.Interparticulate interaction and settling property can be measured by Hausner ratio.

**Hausner ratio= Tapped density/ Bulk density**

**Hausner ratio= Vo/Vf**

Where, Vo= Unsettled apparent volume, Vf=Final tapped volume.

**6) Particle Size Distribution**

Particle size distribution can be determined by sieving method.

**B) Post-compression parameters[14-17]**

**1) Tablet Thickness**

In this three tablets are randomly taken and then their thickness and diameter are measured by Vernier calliper or by using calibrated screw gauze.

**2) Weight Variation Test**

Twenty tablets are selected and weight of individual tablet is taken. Then the average weight and standard deviation are calculated. Test passes when not more than two tablets deviate from average weight.

**3) Hardness**

Expressed in $kg/cm^2$ and it is checked using Monsanto hardness tester by randomly picking three tablets. Hardness helps in knowing ability of the tablet to withstand mechanical shock during handling of tablets.

**4) Friability**

Ten tablets are selected and weighed and then placed in friabilator apparatus which rotate at 25 rpm speed for 4 minutes. After 4 minutes tablets are weighed again.

$$\% F = [1-(Wt/W)]*100$$

Where, W: Initial weight of tablet, Wt: Weight of tablet after revolution.

If % Friability of tablet is less than 1% then it is considered as acceptable.

**5) Tablet Density**

It is an important parameter in case of floating tablets. If density is less than (1.004) gastric fluid, than only the tablets will float. It is calculated using formula:

$V=\pi r2h$, d = m/v, r = Radius of tablet, h =crown thickness (g/cc), m = Mass of tablet.

**6) Disintegration Time**

In this six tablet is placed in disintegration apparatus containing buffer 0.1N HCl or PBS pH 6.8 and test are carried out at 37$^{o}$C. The time taken by tablet to Disintegrate is noted as disintegration time.

**7) *In-vitro* Dissolution Studies**

Dissolution study is performed using USP paddle apparatus by maintaining optimum temperature i.e., 37$^{o}$C at 50 rpm rotational speed. At various time interval, 5 ml sample is withdrawn and is replaced with same amount of buffer. Amount of drug release is then calculated using respective analytical method.

**8) Floating Lag Time**

It is time interval taken by the tablets to start floating. It should be less than one minute. It is measured by dissolution test apparatus containing 0.1 N HCl (900ml).

**9) Floating Time**

It is the total time taken by which the tablets remain floating in the media.

**10) Drug Content Uniformity**

Ten tablets are taken and powdered equivalent weight of drug dose is taken and is transferred to volumetric flask and then buffer is added and absorbance is determined using U.V spectrophotometer.

**11) Swelling Study**

Initially, tablet is weighed (W1) and placed in a glass beaker, containing 200 mL of 0.1 N HCl, maintained in a water bath at 37 ± 0.5 _C. At different time intervals, the tablet is removed and the excess of liquid is carefully removed by a filter paper. The swollen tablet is reweighed (W2). The swelling index (SI) is calculated using the formula:

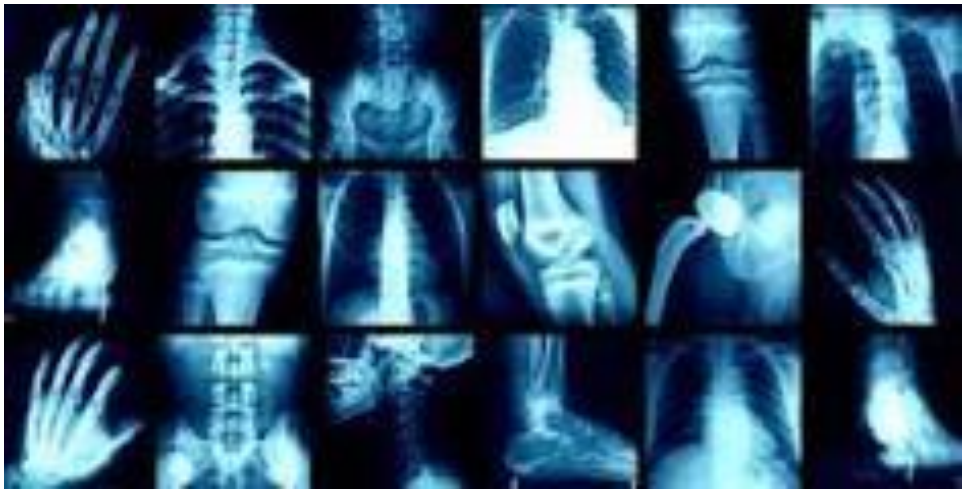
**SI= Wt -W0/W0*100**

Wt= (Weight of swollen tablet), W0= (Initial weight of tablet).

**c) *In-vivo* evaluation[18]:**

**a) Radiology**

X-ray is widely used for examination of internal body systems. Barium Sulphate is widely used Radio Opaque Marker. So, $BaSO_4$ is incorporated inside dosage form and X-ray images are taken at various intervals to view gastric retention.



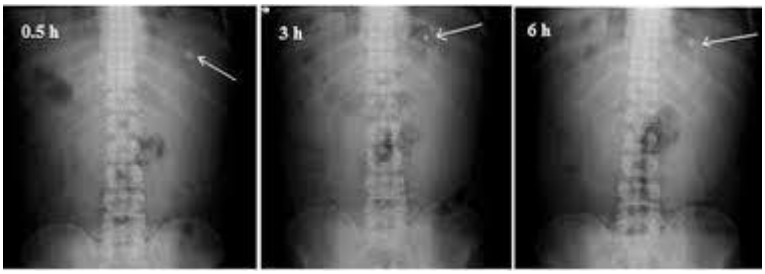



**Figure 5: X-ray study to check gastric retention of tablet**

**b) Scintigraphy**

Similar to X-ray, emitting materials are incorporated into dosage form and then images are taken by Scintigraphy. Widely used emitting material is 99Tc.

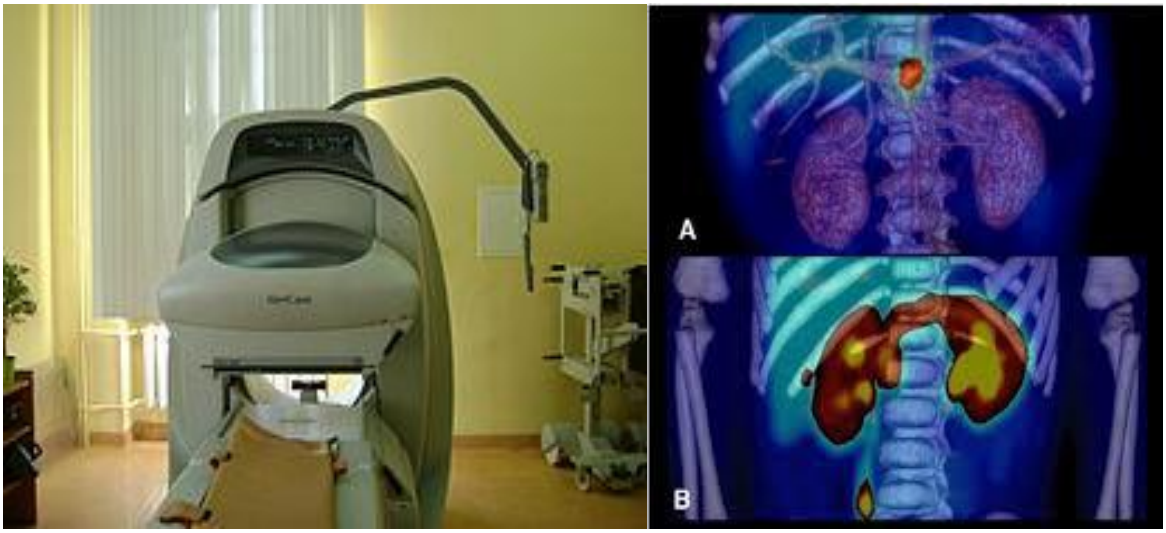



**Figure 6: Scintigraphy study**

**c) Gastroscopy**

Gastroscopy is peroral endoscopy used with fiber optics or video systems. Gastroscopy is used to inspect visually the effect of prolongation in stomach. It can also give the detailed evaluation of GRDDS.

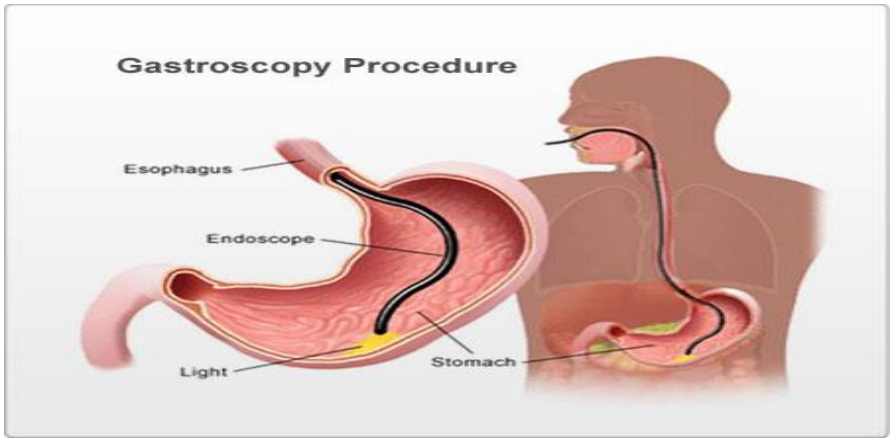



**Figure 7: Gastroscopy study**

**d) Magnetic Marker Monitoring**

In this technique, dosage form is magnetically marked with incorporating iron powder inside, and images can be taken by very sensitive biomagnetic measurement equipment. Advantage of this method is that it is radiation less and so not hazardous.

**e) Ultrasonography**

It is not widely used as it is not traceable at intestine.

**Figure 8: Ultrasonography**

**f) 13C Octanoic Acid Breath Test**

13C Octanoic acid is incorporated into GRDDS. In stomach due to chemical reaction, octanoic acid liberates $CO_2$ gas which comes out in breath. The important Carbon atom which

will come in $CO_2$ is replaced with 13C isotope. So time up to which $13CO_2$ gas is observed in breath can be considered as gastric retention time of dosage form. As the dosage form moves to intestine, there is no reaction.

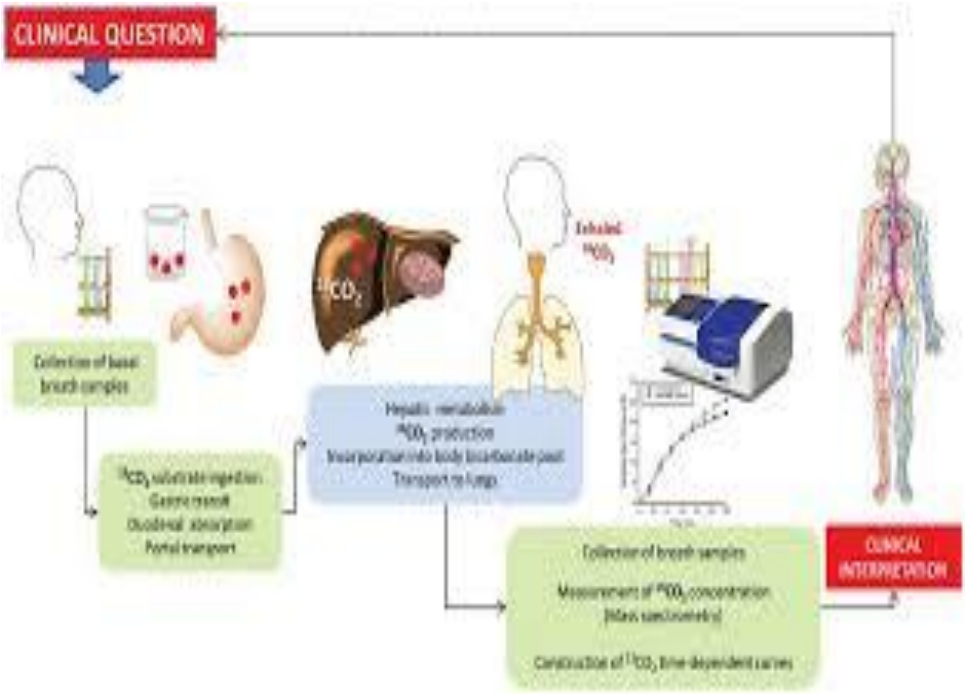



**Figure 9: 13C Octanoic Acid Breath Test**

## CONCLUSION

Bilayer floating tablet dosage forms demonstrate gastric retention of drug and drug release of both immediate and sustained release which provide loading dose as well as enables the prolonged and continuous input of drug to stomach and improve the bioavailability of medication. FBDDS approach may be used for various potential active agents with narrow absorption window, e.g. antiviral, antifungal and antibiotic agents (sulphonamides, quinolones, penicillins, cephalosporins, aminoglycosides and tetracyclines) which are absorbed from very specific regions of GI tract and whose development has been halted due to the lack of appropriate pharmaceutical technologies. So Pharmaceutical industries are trying to prepare one of the most economic and conventional dosage forms, and Floating bilayer tablet is best then any other approaches. In addition, by continual supplying the drug to its most efficient site of absorption, the dosage form may allow for more effective oral use of peptide and protein drugs such as calcitonin, erythropoietin, vasopressin, insulin, low molecular weight heparin, and LHRH. Some of the unresolved critical issues related to the

rational development of FBDDS include the quantitative efficiency of floating delivery systems in the fasted and fed states and the correlation between prolonged GRT and SR/PK characteristics. However, we are as close as we have ever been to see a greater transition of gastric retention devices from commercial method.

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