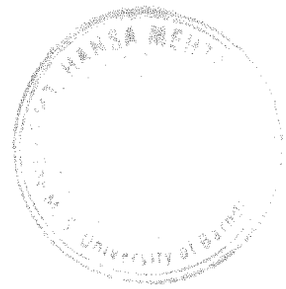


# Chapter VI
# Floating Drug Delivery
## Approach II

## VI.1 INTRODUCTION

Drug delivery system that floats immediately upon contact with gastric fluids present promising approaches for increasing the bioavailability of drugs with absorption windows in the upper small intestine. However, immediate floating can only be achieved if the density of the device is low at the very beginning. Devices with an initially high density (which decreases with time) first settle down in the stomach and, thus, undergo the risk of premature emptying. Inherent low density can, for example, be provided by the entrapment of air (e.g. hollow chambers [Nakamichi et al,2002; Roy Major,1977; Mitra ,1984; Wong et al,1993; Kouichi et al,1994) or by the additional incorporation of low density materials (e.g. fatty substances or oils [Koichi et al, 1986; Willi et al,1989], or foam powder (Streubel et al,2003;2002).

In addition combinations of approaches have been devised to provide additional advantage to floating drug delivery. They are:

- Gas generated devices which increase in size and float due to their low density (Ichikawa et al, 1991; Ichikawa et al, 1989).
- Another approach is combining the concepts of floating and bioadhesion (Nur et al, 2000; Rosa et al, 1994).

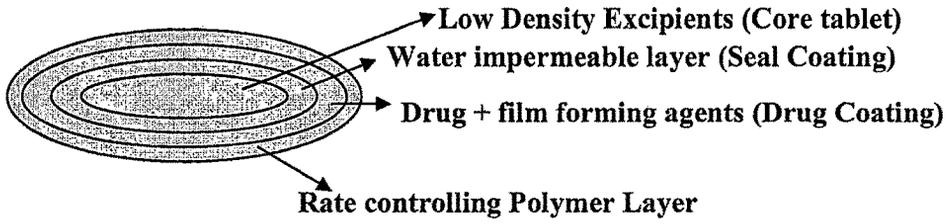
Keeping in view all the above mentioned concepts and learning, it was found that

- Addition of low density excipients such as foam powder or fatty substances can modulate drug release profile.
- Uncoated tablets compressed along with low density excipients should be compressed at low hardness so that air remains entrapped in the pores but these tablets have high friability.
- Combining gas generating system with swelling has the disadvantage that a lag time will occur in gas generation and subsequent swelling over a period of time will modulate drug release profile depending upon the degree of hydration and swelling.
- Combining bioadhesion with floating has the possibility that dosage form might adhere to stomach base instead of floating and also failure of any bioadhesive formulation to prolong gastric residence time has been attributed to insufficient strength of the bioadhesive bond to overcome the strong propulsive forces of the gastric wall and the continuous mucus production and high mucus turnover within the gastric mucosa.

So, the following approach was devised which bypasses all the above disadvantages.

A Pharmaceutical composition comprising of

a) A dummy core tablet with low density excipients;
b) Seal coating over dummy core tablet;
c) Drug coating over seal coated tablet;
d) Release controlling agent coating over drug coated tablet.




**Advantages of this approach**

- A dummy core tablet compressed at low hardness with low density excipients has the advantage that it will immediate float in water and as it is a dummy tablet drug release profile will not be modulated .In order to provide an addition advantage tablet were compressed with diameter of 11 mm so that a dual mechanism of size and floating can be taken as an advantage.
- Seal coating over dummy tablet will provide the advantage that water will not seep inside and change the density of the tablet but coating a low hardness tablet is difficult due to its high friability but it can be overcome with slight precautions taken during coating.
- A drug coating was done over seal coating and further coated with a pH-independent non –swelling polymer to provide controlled drug release.

## *VI.2 MATERIAL*

**Table VI. 1 List of Materials along with specifications and Manufacturer details**

| Ingredients | Specification | Manufacturer |
|---|---|---|
| **Active** | | |
| Alfuzosin HCL | Ph.Eur | Torrent Pharmaceutical Ltd. |
| **Excipients** | | |
| Microcrystalline Cellulose (Avicel pH 102) | NF | FMC Biopolymer |
| Hypromellose( K4M) | NF | Dow chemicals |
| Hypromellose (K100MCR) | NF | Dow chemicals |
| Hydrogenated Castor oil(Cutina HR) | NF | |
| Polyvinyl pyrolidone (PVP K-30) | USP | ISP Technology |
| Colloidal Silicon Dioxide(Aerosil 200) | USP | Degussa |
| Magnesium Stearate | NF | Ferro |
| Lactose anhydrous (Pharmatose DCL21) | USP | DMV international |
| Ethyl cellulose (50 cps) | NF | Hercules |
| Ammonio methacrylate co-polymer Type A (Eudragit RS PO) | NF | Rohm -Gmbh |
| Ammonio methacrylate co-polymer Type B (Eudragit RL PO) | NF | Rohm -Gmbh |
| Triethylcitrate | | |
| **Solvents** | | |
| Isopropyl Alcohol | USP | Finar |
| Acetone | NF | Finar |
| Methylene Chloride | NF | Finar |
| Methanol | NF | Finar |

## *VI.3 METHOD*

### VI.3.1 Selection of Excipients and Process

**Core**

In order to develop an immediate floating core various low density excipients were tried in different ratios and compressed at various hardness in order to access the effect of hardness on floating. Tablets were evaluated for various parameters like hardness, thickness, friability, surface appearance and floating behavior.

**Barrier**

Generally speaking, in order for a Hydrodynamically balanced system (HBS) dosage form to float in the stomach, the density of the dosage form should be less than the gastric contents. A density of less than 1.0 g/ml has been reported in the literature. However, the floating force kinetics of such dosage forms has shown that the bulk density of a dosage form is not the most appropriate parameter for describing its buoyant capabilities. The buoyant capabilities are better represented and monitored by resultant-weight measurements and swelling experiments (Gerogiannis et al, 1993). This is because the magnitude of floating strength may vary as a function of time and usually decreases after immersion of the dosage form into the fluid as a result of the development of its hydrodynamic equilibrium (Timmermans et al, 1990).

In order to prevent water permeation in the core and change in density with time, a barrier layer of water impermeable polymer was coated on core and Ethyl cellulose was used for this purpose. Literature suggests that ethylcellulose when dissolved in an organic solvent or solvent mixture can be used on its own to produce water-insoluble films. Also high viscosity ethyl cellulose grades tend to produce stronger and more durable films. So, ethyl cellulose (50 cps) was used and methylene chloride was used as solvent to dissolve the polymer. The films were prepared with and without a plasticizer. As Triethyl citrate is one of the most versatile plasticizer, it was used for preparing the films. It was found that the films prepared with triethyl citrate were better and easily stretched than films without the plasticizer.

Tablets were coated with different polymers and with different percentage of barrier coating. Barrier coated tablets were placed in a beaker filled with water and barrier properties were observed at different time intervals.

**Drug Coating**

For adherence of drug over barrier layer, polyvinyl pyrrolidone (PVP K-30) was used as film forming agent as both drug and polyvinyl pyrrolidone easily dissolves in common solvent, methanol.

**Polymer Coating**

Eudragit RSPO and RLPO were used as release controlling agent as literature suggest that they are pH –independent non-swelling polymers.

## VI.3.2 Procedure for Tablet preparation

Based on above results, a final formulation was developed with the procedure given below:

**Core tablet**

Step 1. Hydroxy propyl methylcellulose (K100 MCR), Microcrystalline cellulose (pH 102) and Colloidal silicon dioxide were sifted through 40#.
Step 2. Magnesiun stearate was sifted through 60#.
Step 3. Step 1 + Step 2 excipients were mixed together in conta- blender.
Step 4. Blend of Step 3 was compressed in rotary compression machine fitted with 1.11 cm standard concave plain punches.

**Barrier Coating**

Step 5. Triethyl citrate was dissolved in solution of methylene chloride and methanol.
Step 6. Ethyl cellulose (50 cps) was dispersed and dissolved in solution of step 5 while stirring.
Step 7. Coating solution of step 6 was sprayed on core tablet (of step 4) in neo-coata coating machine.

**Drug Coating**

Step 8. Poly vinyl pyrrolidone (K-30) was dissolved in methanol.
Step 9. Alfuzosin HCl was added to solution of step 8 and dissolved.
Step 10. Coating solution of step 9 was sprayed on barrier coated tablet (of step 7) in neo-coata coating machine.

**Polymer Coating**

Step 11. Talc and Colloidal silicon dioxide were dispersed in part of Isopropyl alcohol in colloid mill.
Step 12. Isopropyl alcohol and acetone were separately mixed and Triethyl citrate was dissolved in it.
Step 13. Eudragit RLPO was added in solution of step 12 and dissolved while stirring.
Step 14. Eudragit RSPO was added in solution of step 13 and dissolved while stirring.
Step 15. Dispersion of step 11 and solution of step 14 were mixed while stirring.
Step 16. Dispersion of step 15 was sprayed on drug coated tablets (of step 10) in neocoata coating machine.

## VI.3.3 Process and formulation optimization

Process optimization of each step (core formulation, barrier coating, drug coating and polymer coating) was carried out and dissolution studies were carried out in 0.1 N HCl/Basket/100 rpm.

## VI.3.4 Gastric Residence Time

**Preparation of Barium tablets**

Granulation was conducted with the procedure same as that followed to prepare tablets with size exclusion technology (non-swelling) (Chapter V). For floating drug delivery, Barium sulphate tablets were compressed with multi-tip punch (6 tips of diameter of 1mm each) at tablet weight of 10 mg.

Three tablets of Barium sulphate each of 10 mg were placed inside the dummy core tablet formulation of B.No 06, which was further seal coated followed by polymer coating.

**Protocol of the Gastric Residence Time study**

Protocol was followed same as that followed in Approach IA (size exclusion technology (non -swelling) (Chapter V).
Gastric residence time was carried in four healthy volunteers (2 for fasted and 2 for fed state).

## VI.4 RESULTS

**Table VI. 2 Comparative formulation of B.No. 01, B.No 02 and B.No 03 for development of core tablet**

| Ingredients | Mg/tablet | | |
|---|---|---|---|
| | B.No.01 | B.No.02 | B.No.03 |
| Microcrystalline Cellulose (Avicel pH 102) | 179.49 | 200.00 | 168.33 |
| Hypromellose( K4M) | 72.68 | 81.00 | |
| Hypromellose (K100MCR) | ..... | ..... | 75.00 |
| Hydrogenated Castor oil(Cutina HR) | 35.90 | ..... | ..... |
| Lactose anhydrous (Pharmatose DCL21) | 53.85 | 60.00 | ..... |
| Colloidal Silicon Dioxide(Aerosil 200) | 4.71 | 5.25 | 4.38 |
| Magnesium Stearate | 3.37 | 3.75 | 2.29 |
| **Total weight of the core** | **350.00** | **350.00** | **250.00** |

**Table VI. 3 Characterization and Behavior of core tablets of B. No. 01, B.No 02 and B. No 03**

| Parameters | B.No.01 | B.No.02 | B.No.03 |
|---|---|---|---|
| Hardness (N) | 22-32 | 20-34 | 25-41 |
| Thickness (mm) | 4.85-4.93 | 5.01-5.19 | 4.01-4.13 |
| Friability (%) | 0.43 | 2.06 | 0.32 |
| Surface appearance | Pitted surface | Surface more pitted | Smooth surface |
| Floating behavior | Floats | Floats | Floats |

Formula of B.No. 03 as core was used for further development as friability was lower and surface was much smoother than other formulations (B.No. 01 and B.No. 02).So, adherence of seal coating film to the smooth surface will be better and also pin holes and tablet breaking during seal coating process will be less.

For Barrier coating different hydrophobic excipients were tried, like- Hydrogenated castor oil, Ceto stearyl alcohol and Ethyl cellulose. Hydrogenated castor oil was found to be less tacky (i.e. adherence of film of hydrogenated castor oil to core tablet was less) as compared to Ceto stearyl alcohol and Ethyl cellulose. Core tablets when coated with cetostearyl alcohol and dried, melting of the coating of cetostearyl alcohol was observed (as melting range of ceto stearyl alcohol is 48 °C -55°C).Ethyl cellulose films were found to be most satisfactory and were used for further development.

**Table VI. 4 Barrier properties of different % of coating of Ethyl cellulose (10 cps) at different time intervals**

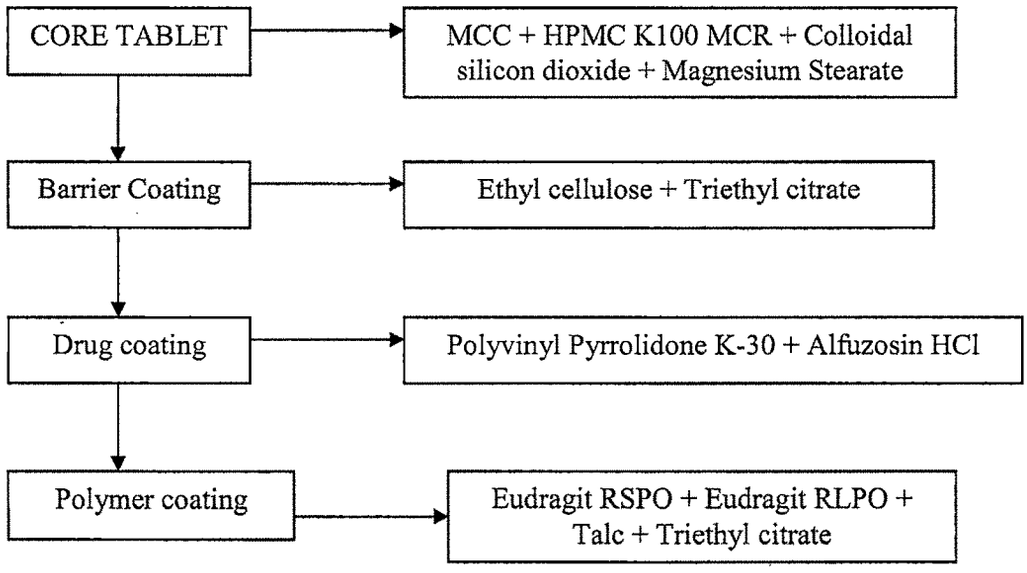
| Time points | % of Barrier Coating | | |
|---|---|---|---|
| | 3 | 5 | 10 |
| Initial | Intact | Intact | Intact |
| After 4 hrs | Barrier broken | Intact | Intact |
| After 5 hrs | Barrier completely peeld off | Barrier started breaking from sides of tablet | Intact |
| After 8 hrs | Tablet started swelling | Barrier started peeling off from tablet surface | Barrier started breaking from sides of tablet |
| After 24 hrs | A gel mass formed | Swelling less compared to 3% coating | Tablets swelled least |

Therefore barrier coating of (9 %) with Ethyl cellulose (50 cps) was tried and it was observed that barrier propertied remain intact for 30 hrs.

**Table VI. 5 Final composition of B.No. 06**

| S.No. | Ingredients | mg/tab |
|---|---|---|
| | **CORE** | |
| 1 | Microcrystalline Cellulose (Avicel pH 102) | 168.33 |
| 2 | Hypromellose (K100MCR) | 75.00 |
| 3 | Colloidal Silicon Dioxide (Aerosil 200) | 4.38 |
| 4 | Magnesium Stearate | 2.29 |
| | **Total** | **250.00** |
| | **BARRIER COATING** | |
| 5 | Ethyl Cellulose (50 cps) | 19.57 |
| 6 | Triethyl citrate | 2.94 |
| 7 | Methanol:Methylene Chloride(2:8) | q.s. |
| | **Total** | **272.51** |
| | **DRUG COATING** | |
| 8 | Alfuzosin HCl | 10.00 |
| 9 | Polyvinyl pyrolidone (PVP K-30) | 3.00 |
| 10 | Methanol | q.s. |
| | **Total** | **285.51** |
| | **POLYMER COATING** | |
| 11 | Ammoniomethacrylate copolymer type B (Eudragit RSPO) | 2.50 |
| 12 | Ammoniomethacrylate copolymer type A (Eudragit RLPO) | 1.50 |
| 13 | Triethyl citrate | 0.52 |
| 14 | Talc | 3.00 |
| 15 | Isopropyl alcohol: Acetone (6:4) | q.s. |
| | **Total** | **293.03** |

Flow Chart




## Process optimization

### Core

In order to see the effect of Compression on Hardness, a blend was prepared of 5000 tablets and compressed at different hardness and their floating behavior was observed:

### Barrier

For Barrier coating 1.8 kg core tablets were loaded in 3 kg pan of neo-cota coating machine and Ethyl cellulose was dissolved in methylene chloride because of its high solubility in this solvent.

Due to high friability of the core tablet, abrasion of the tablet occurred during coating. This was resolved by keeping the pan rpm at low speed, high spray rate and high atomization during initial coating. As methylene chloride has low boiling point (40°C), frequent gun chocking was observed. Addition of methanol to methylene chloride (2:8 ratio) solved the problem of gun chocking as the solution boiling temperature was raised the boiling point of methanol is high (64.7 °C).

### Drug Coating

Drug and Polyvinyl pyrolidone (K-30) were dissolved in methanol and coated over barrier coated tablets. Content uniformity of the tablet was evaluated to access uniformity

of coating. It was found that although RSD of content uniformity from batch to batch was only 2.74-3.5 % well below 5% limit as per regulatory guidelines. Drug loss was 30-35% from batch to batch .So overages of 35% were added in further batches in drug coating solution.

## Polymer Coating

Eudragit RSPO and RLPO were used in different ratio for controlling the release profile and dissolution was evaluated in 0.1N HCL/Basket/100rpm.

Atomization air pressure of 0.7 bar was set as the tablets were of low density. At high atomization air pressure bumping of tablets was observed.

*Final parameters optimized were:*

**Table VI. 6 Optimized parameters for Core tablet**

| | | | |
|---|---|---|---|
| Hardness (N) | 68-81 | 40-50 | 25-41 |
| Friability (%) | 0.215 | 0.218 | 0.477 |
| Floating Behavior | Does not float | Threshold for floating | Floated immediately |

During the compression at hardness range of 25-41N, tablets were intermittently accessed for their floating behavior by immersing them in 200ml of water .It was found that throughout the compression, the tablets remained floating in the above mentioned hardness range (25-41N).

**Table VI. 7 Optimized parameters for Barrier coating**

| Time (min) | Inlet temp. (°C) | Exhaust temp.(°C) | Pan rpm | Pump rpm | Spray rate(gm/min) |
|---|---|---|---|---|---|
| 0-10 | 55-58 | 30-32 | 2-3 | 10-12 | 35-40 |
| 10-20 | 55-58 | 30-32 | 6-7 | 12-14 | 40-50 |
| 20-till completion | 55-60 | 30-32 | 7-8 | 14-16 | 50-56 |

**Table VI. 8 Optimized parameters for Drug Coating**

| Time (min) | Inlet temp. (°C) | Exhaust temp.(°C) | Pan rpm | Pump rpm | Spray rate(gm/min) |
|---|---|---|---|---|---|
| 0-20 | 42-45 | 35-37 | 7-8 | 7-8 | 7-8 |
| 20-till completion | 44-46 | 35-37 | 7-8 | 7-8 | 8-9 |

**Table VI. 9 Optimized parameters for Polymer Coating**

| Time (min) | Inlet temp. (°C) | Exhaust temp.(°C) | Pan rpm | Pump rpm | Spray rate(gm/min) |
|---|---|---|---|---|---|
| 0-20 | 37-40 | 33-35 | 12-13 | 7-8 | 7-8 |
| 20-40 | 37-40 | 33-35 | 12-13 | 8-9 | 8-9 |
| 20-till completion | 37-40 | 33-35 | 12-13 | 8-9 | 8-9 |

## Dissolution Studies

Dissolution profile was evaluated in 0.1 N HCl/Basket/100rpm.

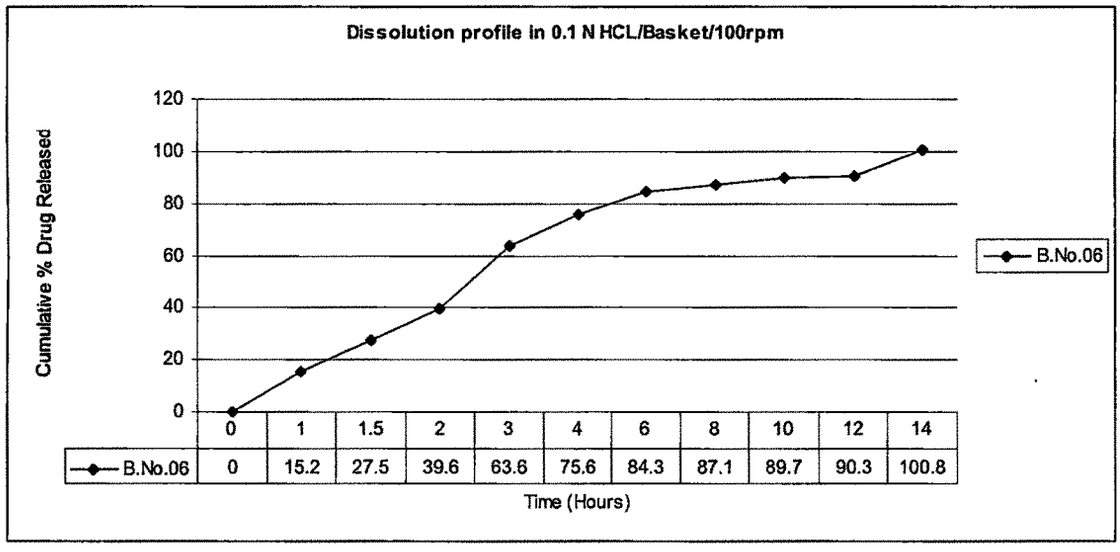


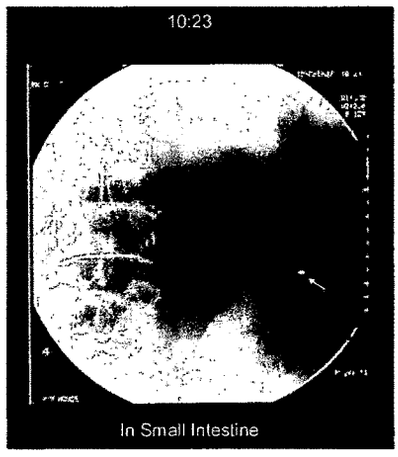

**Figure VI. 1 Dissolution profile in B.No. 06 in 0.1 N HCL/Basket/100rpm**

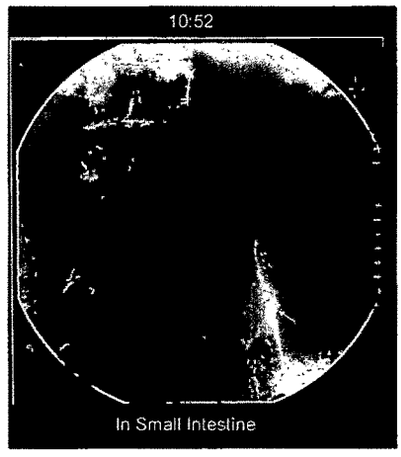
## Gastric Residence Time

**Table VI. 10 Gastric Retention time of Dummy tablets of B.No 06 in Healthy volunteers under Fasted condition**

| | Floating | |
|---|---|---|
| **Time (min)** | **PK-D-737** | **PK-G-085** |
| 0 | Stomach | Stomach |
| 20 | Small Intestine | Stomach |
| 40 | Small Intestine | Small Intestine |
| 60 | Small Intestine | Small Intestine |
| 90 | Colon | Small Intestine |
| 150 | Rectum | Colon |





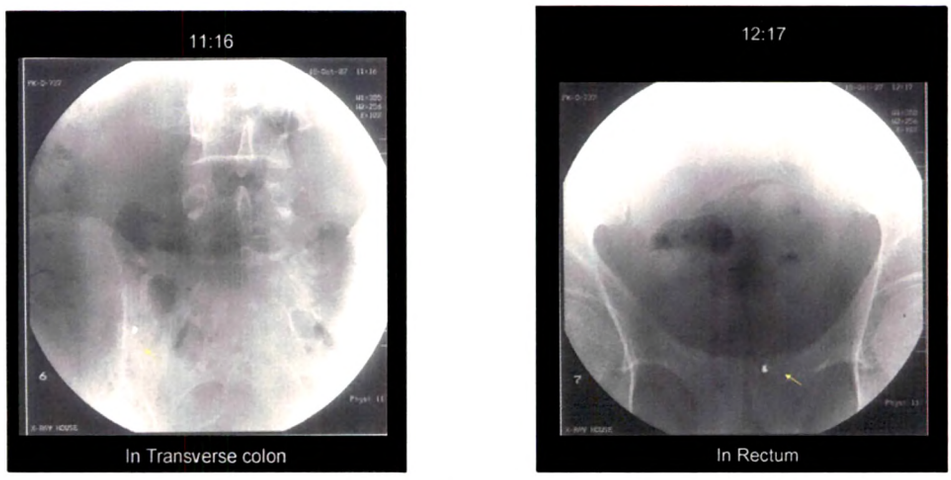
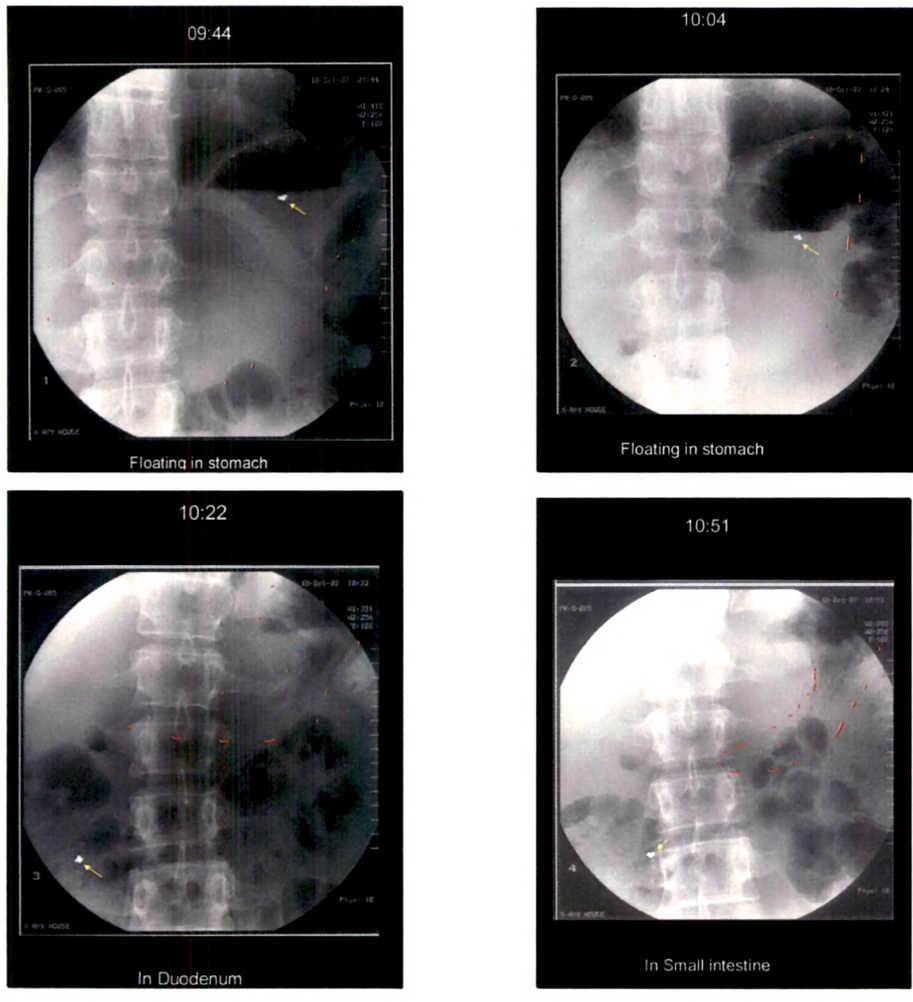



**Figure VI. 2 Gastric Retention time of Dummy tablets of B.No 06 in Healthy volunteer (PK-D-737) under Fasted condition**



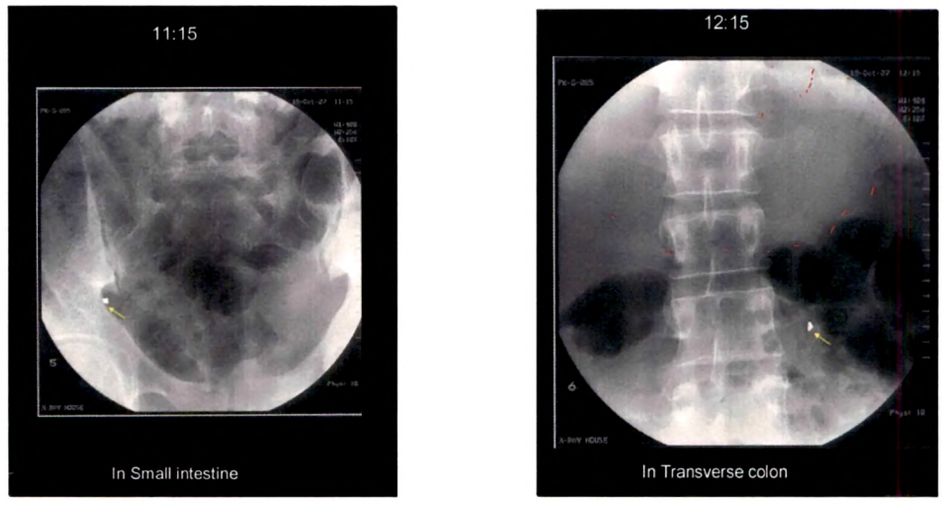
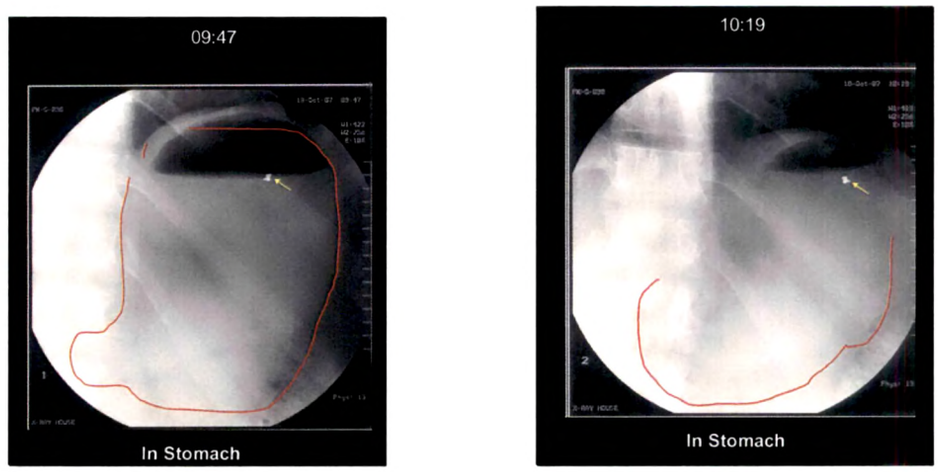
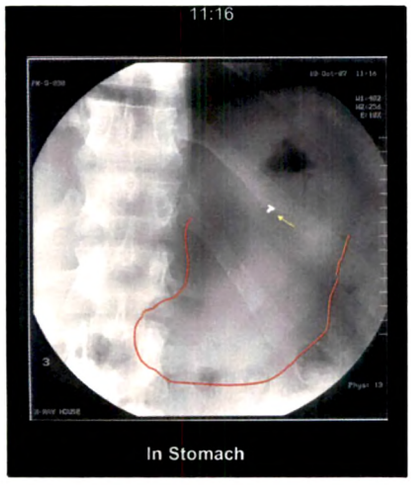



**Figure VI. 3 Gastric Retention time of Dummy tablets of B.No 06 in Healthy volunteer (PK-G-085) under Fasted condition**

**Table VI. 11 Gastric Retention time of Dummy tablets of B.No 06 in Healthy volunteers under Fed condition**

| | Floating | |
|---|---|---|
| **Time (hr)** | **PK-G-098** | **PK-G-105** |
| 0 | Stomach | Stomach |
| 0.5 | Stomach | Stomach |
| 1.5 | Stomach | Stomach |
| 2.5 | Stomach | Stomach |
| 2.6 | Stomach | Small Intestine |
| 3.5 | Stomach | Small Intestine |
| 4.5 | Stomach | Small Intestine |
| 5.5 | Stomach | Small Intestine |
| 6.5 | Stomach | Colon |

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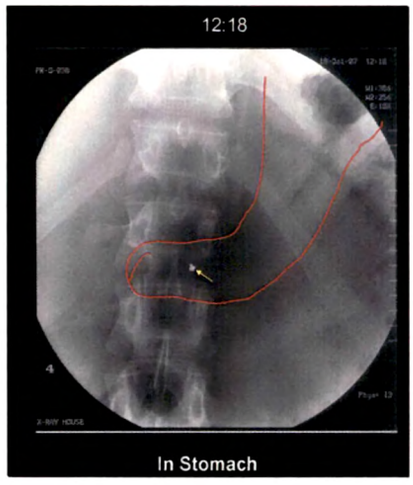
In Stomach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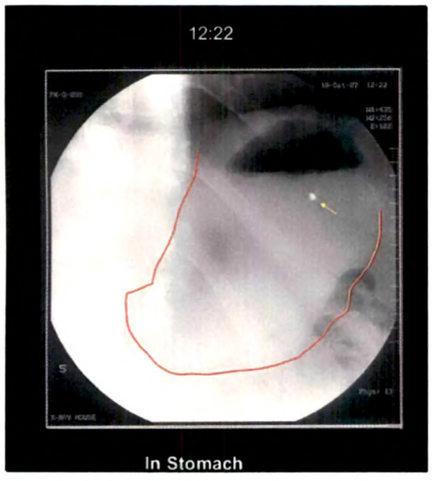
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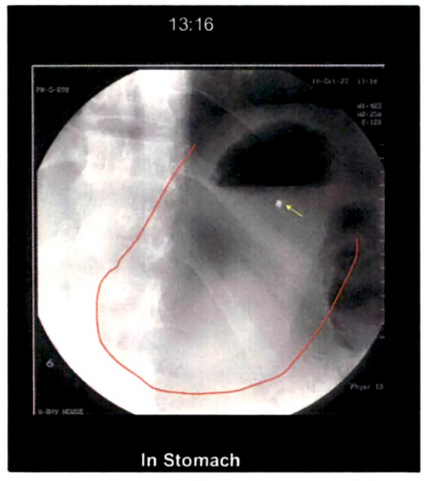
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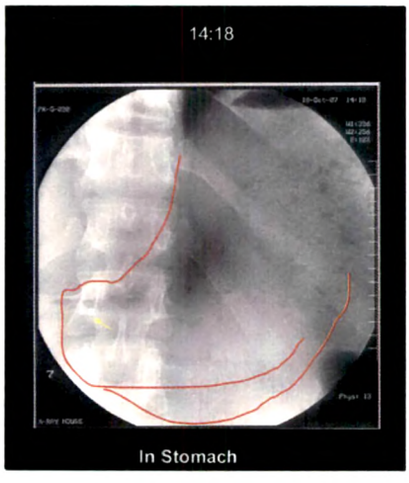
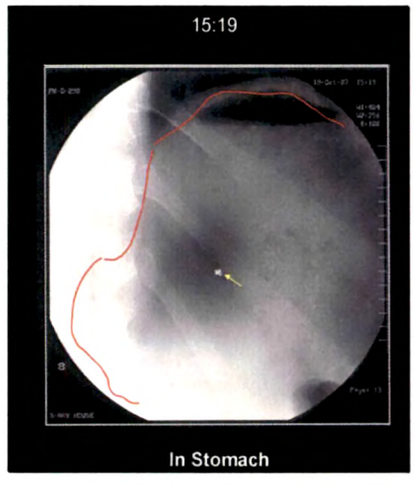

14:18
In Stomach


15:19
In Stomach

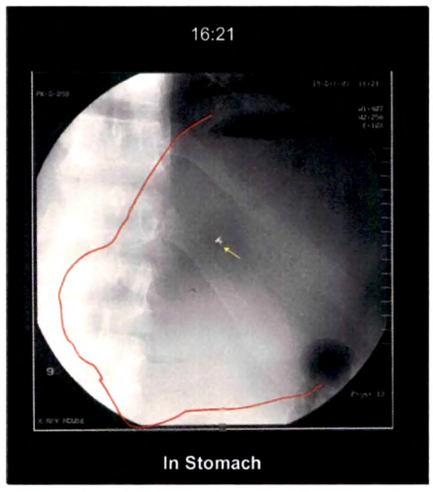
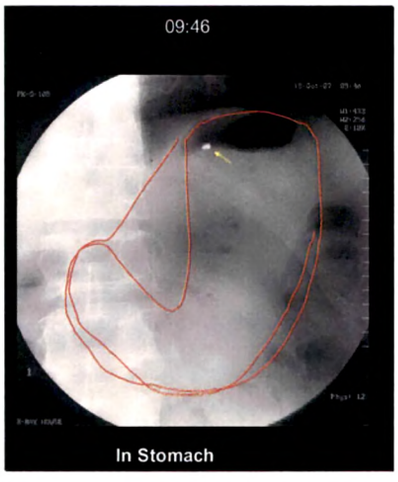
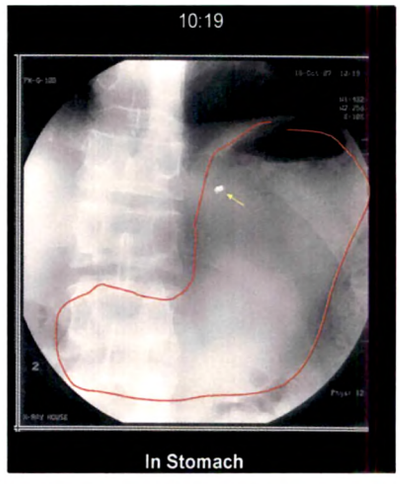
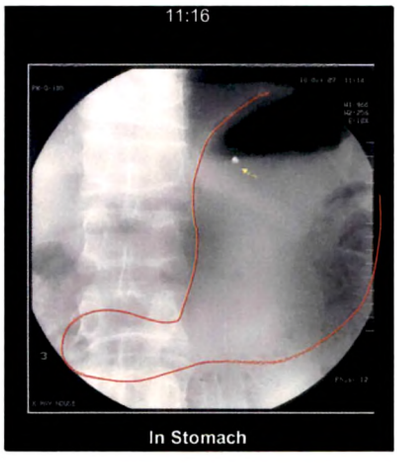
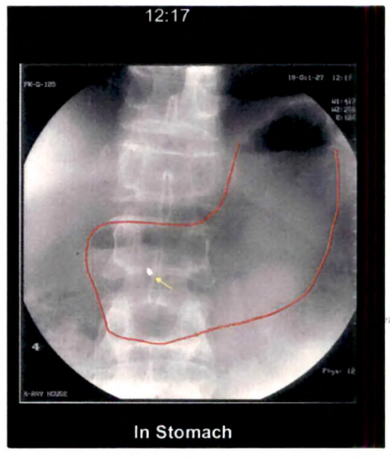



**Figure VI. 4 Gastric Retention time of Dummy tablets of B.No 06 in Healthy volunteer (PK-G-098) under Fed condition**



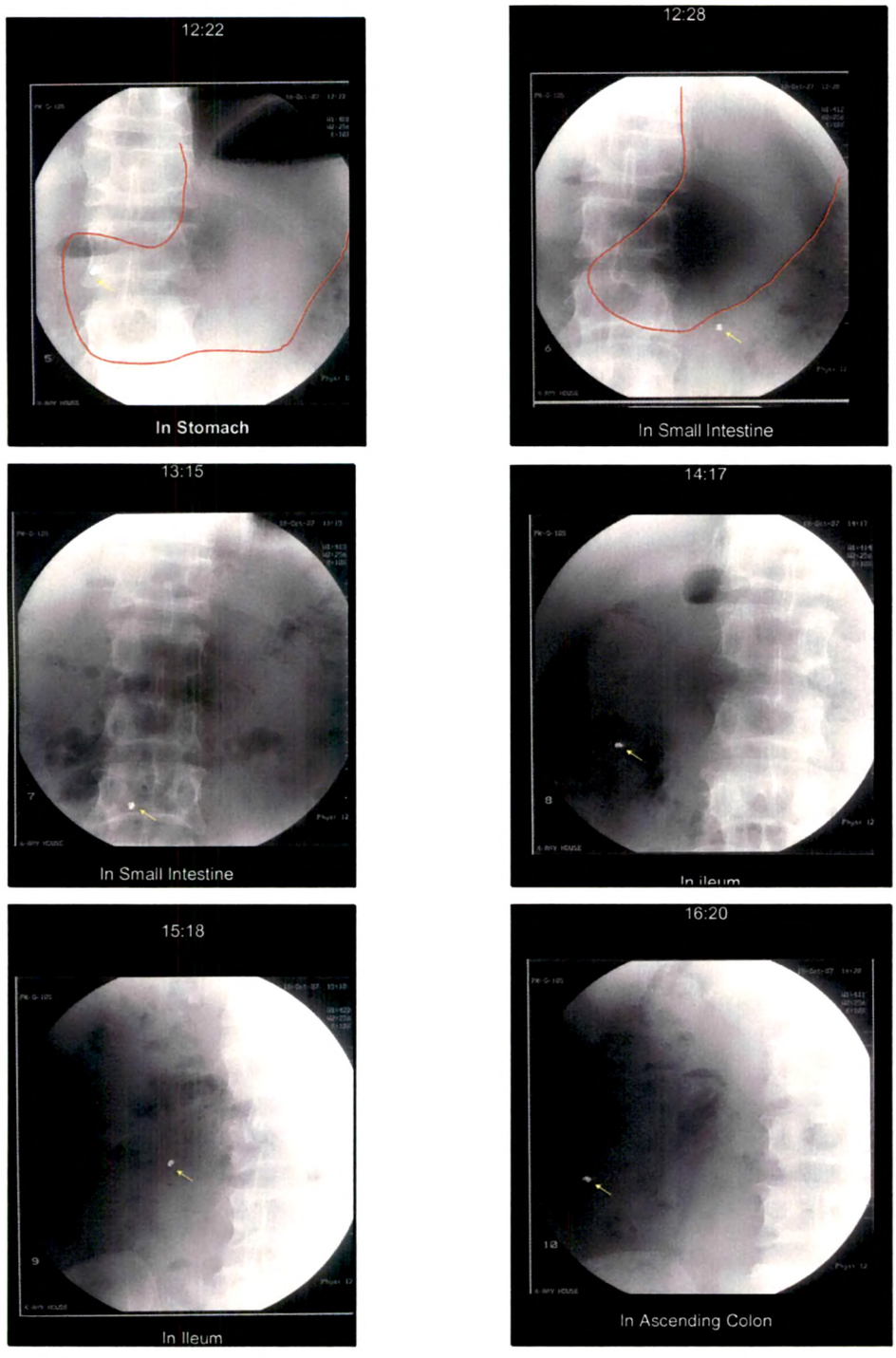



**Figure VI. 5 Gastric Retention time of Dummy tablets of B.No 06 in Healthy volunteer (PK-G-105) under Fed condition**

In the fasted state, gastric retention was 0-20 min for one volunteer and 20-40 min in second volunteer. The tablets in both the volunteers passed into colon in 60-90 min for one volunteer and 90-150 min for the other. Average gastric residence time was estimated to be 30 min.

In the fed state gastric retention time was 6.5 hours in one of the volunteers and 2.5-2.6 hours for the other. Average gastric residence time was estimated to be 4.5 hrs.

As the water restriction was only till 2 hrs post dose, the volunteers were free to consume water at their will. It was found that in fed state, volunteer (PK-G-098) consumed water after 2.15, and 5.05 hrs whereas the other volunteer (PK-G-105) consumed only at 4.5 hrs post dose. Water was also consumed by both the volunteers with food which was served to the fed state volunteers at $4^{th}$ hour, post dose.

None of the tablets disintegrated during the study period in both the fasted and fed state and no discomfort or untoward reaction was reported by any of the volunteer.

## *VI.5 DISCUSSION*

Floating drug delivery system (FDDS) or hydrodynamically balanced systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. FDDS are retained in the stomach for a prolonged period of time by virtue of their floating properties; however, the formulation should immediately float upon immersion in the fluid so that the formulation remains well away from the pyloric sphincter.

Microcrystalline cellulose and Hypromellose are very low density excipients with bulk density of 0.33 gm/ $cm^3$ and 0.34 gm/ $cm^3$ respectively and to have directly compressible formulation, Hypromellose K100 MCR grade was used. According to literature, Microcrystalline cellulose acts as a dry binder also (Rowe et al, 2003). So, core tablets were compressed at low hardness, so that tables float immediately on immersion in water (due to air entrapped in between the blend of excipients). Friability of the tablets was found to be approximately 0.5%.

Barrier coating with Ethyl cellulose (50 cps) maintained the tablet integrity for over 30 hrs.Drug coating with polyvinyl pyrrolidone (K-30) as film forming agent was used and adherence of the film was found to be good.

A combination of polymers, Eudragit RSPO and RLPO were used to get the desired release profile and Eudragit RSPO:RLPO::60:40 ratio was found to be optimum. As the tablets float immediately on immersion in dissolution media, liquid-tablet interface contact will be less i.e. surface area exposed will be less and as Eudragit polymers are hydrophobic polymers, so a faster dissolution profile was optimized.

X-Ray photographs of gastric retention study, showed that tablets floated immediately after fluid intake.

In the fasted state, tablets remained in the stomach for a short duration (average of 30 min) because of faster emptying time of the liquid through the pylorus. In the fed state, tablet remained high above the pylorus as observed in X-Ray photographs. During the study, slight variation in buoyancy of the tablet was observed. As the formulation studied was a non-disintegrating, non-swelling dosage form, the change in buoyancy might be due to viscous chyme adhering the tablet surface pushing it downwards but still the buoyant force of the tablet dominated the gravitational force. Possible reason for low gastric retention (2.5-2.6 hours post dose) for volunteer (PK-G-105) might be due to the fact that he had not taken water at 2.15 hours post dose and when exposed to X-ray radiation at 2.5 hours post dose, liquid and food had completely emptied from the stomach and the tablet was very near to pylorus and when exposed at 2.6 hours, post dose, tablet emptied into the small intestine whereas the other volunteer (PK-G-098) who had taken water at 2.15 hours post dose, tablets floated again due to buoyancy as observed in X-Ray photograph taken at 2.54 hours and 2.6 hours post dose. Food was taken along with water at 4 hours post dose by both the volunteers and thereafter water was taken at 5.05 hours post dose by volunteer (PK-G-098). This provided buoyancy to

the tablet and it remained in the stomach for longer period of time in that volunteer (PK-G-098) as compared to volunteer PK-G-105.

Thus food along with water provided greater residence time in volunteer (PK-G-098) as compared to the volunteer (PK-G-105) who had not taken water at 2.15 hour post dose. Considering the role of specific gravity in gastric residence time (GRT), the potential of food in modifying GRT can not be overlooked .Similar observations have been made by other workers.

One of the earlier in vivo evaluations of floating drug delivery system (FDDS) by Muller-Lissner et al. (1981) demonstrated that a GRT of 4–10 h could be achieved after a fat and protein test meal. Furthermore, food affects the GRT of dosage forms depending on its nature, caloric content and the frequency of intake (Oth et al, 1992; Moore et al, 1984; Mojaverian et al, 1985). For example, Oth et al. (1992) reported that the mean GRT of a bilayer floating capsule of misoprostol was 199±69 min after a single light meal (breakfast). However, after a succession of meals, the data showed a remarkable prolongation of the mean GRT, to 618±208 min. In another study, Iannuccelli et al. (1998) reported that in the fed state after a single meal, all the floating units had a floating time (FT) of about 5 hour and a GRT prolonged by about 2 h over the control. However, after a succession of meals, most of the floating units showed a FT of about 6 hour and a GRT prolonged by about 9 hour over the control, though a certain variability of the data owing to mixing with heavy solid food ingested after the dosing was observed. Interestingly, most of the studies related to effects of food on GRT of floating drug delivery system (FDDS) share a common viewpoint that food intake is the main determinant of gastric emptying, while specific gravity has only a minor effect on the emptying process (Davis et al, 1986; Mazer et al, 1988; Sangekar et al, 1987; Muller-Lissner et al, 1981). Stated otherwise, the presence of food, rather than buoyancy, is the most important factor affecting GRT and floating does not invariably increase GRT. In fact, studies have shown that the gastric emptying time (GET) for both floating (F) and non-floating (NF) single units are shorter in fasted subjects (less than 2 h), but are significantly prolonged after a meal (around 4 h) [Davis et al.,1986; Muller-Lissner and Blum ,1981]. In a similar study, Agyilirah et al. (1991) found that in the fed state, balloon (floating) tablets prolonged the GET by an average of 6 h over that of uncoated, non-disintegrating tablets; however, in fasted state, the balloon tablets did not significantly prolong gastric emptying time (GET) and both tablets had much shorter emptying times compared to the fed state. Thus, in view of foregoing discussions, it may be concluded that although floating systems possess an inherent ability for gastric retention, they rely more on the presence of a meal to retard their emptying. Gastric emptying depends on the onset of the migrating motor complex (MMC). Therefore, the GRT is significantly increased under fed conditions, since the onset of MMC is delayed (Desai et al, 1993).

Gastric retention time values were found to highly variable in both sets of volunteers evaluated in fasted and fed state. Therefore it is more likely that drug delivery by this system might result in variable plasma drug concentrations. So bioavailability studies were not carried out with this formulation approach.

## *VI.6 CONCLUSION*

The present formulation designed had obvious advantage of immediate floating as soon as it is immersed in fluid as observed both in in-vitro and in vivo studies. In addition as it is a non- disintegrating, non-swelling dosage form, magnitude of floating strength had not varied as a function of time. Thus the density of the dosage form had remained well below the density of the fluids throughout the study period both in vitro and in vivo.

Floating system requires fluid in the stomach to function. The resting volume of the stomach is 25 to 50 ml. After intake of 200ml of water along with formulation, the volume increases to nearly 250 ml. The emptying of non-caloric liquids begin immediately and is directly proportional to the volume present in the stomach in a first order exponential process with a half-emptying time of 15-20 min., where the gastro-duodenal pressure gradient is the driving force (Hunt et al, 1951; Collins et al, 1983; Smith et al, 1984; Marzio et al, 1991; Caballero-Plasencia et al., 1999).So, in the fasted stomach the amount of liquid is not sufficient for the buoyancy of drug delivery system and the stomach's entire contents are emptied down to the small intestine within 2–3 h because of the typical phase III activity (Rubinstein et al, 1994). Despite of having a diameter of 11mm along with floating property, tablets emptied within 30 min on an average in fasted state showing that in fasted state floating drug delivery is not suitable for gastric retentive drug delivery.

While in the fed state the gastric retention was prolonged significantly. In one of the volunteers who had taken water intermittently in between the food hours, tablet remained in the stomach till the study duration i.e. 6.5 hours post dose whereas the other volunteer who had not taken water, tablet remained till 2.5-2.6 hours post dose. High fat breakfast which was taken half an hour before dose might have emptied during this period. As the tablet size was large, this would have provided an additional advantage for prolonging the gastric retention time. Therefore not only food but intermittent uptake of fluid in-between meals) might be useful for prolonging the gastric residence time.

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