INTRODUCTION

1.1 Gastric Cancer In Indian Context
1.2 Combination Chemotherapy
1.2 Stomach Or Site Specific Therapy
1.4 Floating Drug Delivery System
1.5 Research Envisaged
1.6 Proposed Methodology During Tenure Of Research Work
1.7 Literature Surveyed
1.1 GASTRIC CANCER IN INDIAN CONTEXT

Gastric cancer is the second most common cancer and cause of cancer related death world wide. Gastric cancer was the leading cause of cancer death in men and third leading cause of cancer of women\(^{(1,2)}\). India is a developing country with one of the most diverse populations and diets in the world. Cancer rates in India are lower than those seen in the western countries, but are rising with increasing migration of rural population to the cities, increase in life expectancy and changes in the life style. In India there seems to be a difference in the distribution frequency of gastric cancer incidence \(^{(3)}\). The southern and eastern parts of the India have higher frequency of gastric cancer than rest of the country. The large vegetarian population in northern India is at a lower risk of gastric cancer. But the times are changing; rapid flourish of post globalization, fast food brought by corporate culture, germ free bottled water, pasteurized milk and preserved meat items to the present day life in big Indian cities. However, it will be too early to link it with rising gastric cancer incidences in cities in India\(^{(4)}\).

1.1.1. What Is Gastric Cancer

Cancer of stomach is a major subject of the study and research in medical sciences. Cancer of the major organ of the body that holds food for digestion is referred to as gastric cancer. It can develop in any part of the stomach and spread to the other organ. Infection with a bacterium called *Helicobacter pylori* is associated with gastric cancer. The risk of gastric cancer is also increased with Down syndrome\(^{(5)}\).

1.1.2 Signs And Symptoms Of Gastric Cancer

Unfortunately, stomach cancer is asymptomatic during its early stages which can cause an initial diagnosis to be delayed for more than 80 percent of patients. However, some of the initial stomach cancer symptoms are \(^{(6, 7)}\):  

- Indigestion that never goes away and stomach discomfort.
- Bloated feeling right after eating.
INTRODUCTION

• Feeling full too easily.
• Vague discomfort in the abdomen, above the navel.
• Mild nausea and vomiting sensation.
• Loss of appetite.
• Heartburn.

When the cancer advances, stomach cancer symptoms become more severe:

• Stomach pain.
• Vomiting with or without blood.
• Blood in the stool or stool which is black in color.
• Tiredness caused by anemia (due to the stomach walls bleeding).
• Difficulty swallowing.
• Jaundice (the skin and eyes become yellow).
• Ascites (fluid starts to build up inside the abdomen cavity).
• Significant weight loss.

Figure No. 1.1 Gastric Cancer
1.1.3 Types Of Gastric Cancer

There are 5 main types of stomach cancer (gastric cancer) which include\(^8\):

1. **Adenocarcinoma**: This is the most common type of stomach cancer, 90 to 95 percent of stomach cancer cases, and develops in the glandular tissues.

2. **Lymphoma**: This is a rare type of stomach cancer that develops in the immune system tissue of the stomach wall.

3. **Leiomyosarcoma**: This is a type of stomach cancer that develops in the stomach muscle layer.

4. **Gastrointestinal Stomal Tumors**: This type of stomach cancer develops in the tissues which support the digestive organs. This type of tumor develops in the stomach wall tissues that contain a specific type of cell called intestinal cells of Cajal. Gastrointestinal stomal tumors are a rare form of cancer and can occur anywhere in the gastrointestinal tract. However the majority of GIST cases occur in stomach.

5. **Carcinoid Tumors**: This is another less common form of stomach cancer that develops in the hormone-producing tissues of the stomach. Most of these tumors do not spread to other organs.

1.1.4 Stages Of Gastric Cancer

An important prognostic predictor for any type of cancer is the clinicopathologic stage. The most common staging system used for cancer is the American Joint Committee on Cancer (AJCC) TNM system. According to this system, the survival predictors in patients with gastric cancer are: (1) the level of cancer invasion through the stomach wall and (2) the number of lymph nodes affected\(^8,9,10\).

The TNM system refers to: (T) the tumor features - size and invasion level; (N) the involved lymph nodes (lymph nodes are part of the body immune system); and (M) the cancer metastasis - the metastasis stage is the last developmental cancer stage where the
cancer spreads to distal organs (organs situated far from the origin point). Also, each of these dimensions has their own staging system\(^{(11, 12)}\).

**T Stage for gastric cancer**

*Tis (Carcinoma in situ):* According to this stage, cancerous cells are confined to the mucosa tissue (the inner layer of the stomach) without affecting other layers of the stomach.

*T1:* In this stage, the tumor has invaded the submucosa (the inner layer of the stomach located beneath mucosa).

*T2:* In this stage, the tumor has invaded the muscle layer of the stomach or the tissues beneath the serosa (the outer layer of the stomach - the stomach protective membrane).

*T3:* In this stage, the tumor has perforated the stomach's protective membrane without spreading to adjacent organs.

*T4:* In this stage, the tumor has perforated the serosa and has spread to adjacent organs or other anatomic structures (like major blood vessels).

**N Stage of gastric cancer**

*N0:* The cancer has not invaded the lymph node near the stomach.

*N1:* The cancer has invaded 1 to 6 lymph nodes.

*N2:* The cancer has invaded 7 to 16 lymph nodes.

*N3:* The cancer has invaded more then 16 lymph nodes.

**M Stage for gastric cancer**

*M0:* There is no distal metastasis (far distance organs from the origin point are not affected).

*M1:* The cancer has spread to distal organs.
1.1.5 Causes And Risk Factors Associated With Gastric Cancer

The exact causes of stomach cancer are unclear to researchers. Nevertheless, several risk factors have been identified. They include:\(^{(13)}\):

1) *Age*: The risk of developing stomach cancer is higher in people over 40.

2) *Gender*: Men are more likely to develop stomach cancer than women.

3) *Ethnicity*: Stomach cancer is more common among Hispanics, African Americans, Asians, and Pacific Islanders.

4) *Tobacco and alcohol abuse*: The risk of developing stomach cancer is higher in smokers and alcohol abuse. Cigarette smoking and alcohol consumption may exert independent effects on the development of gastric cancer.

5) *Type A blood*: People with type A blood has a higher risk of developing stomach cancer.

6) *Family history*: The risk of developing stomach cancer increases when there is a family history of stomach cancer.

7) *Diet*: A diet rich in smoked food, salted meat and fish, and pickled vegetables increases the risk of developing stomach cancer. However, a diet rich in grain products, fresh fruits and vegetables (that contain vitamin A and C) decrease the risk for stomach cancer.

8) *Obesity*: Overweight or obese people are more likely to develop stomach cancer (especially cancer of the cardia, the upper section of the stomach).

9) *Previous stomach surgery*: People that had part of their stomach removed are at a higher risk for developing stomach cancer.
10) **Medical conditions:** There are approximately eight medical conditions that can increase the risk to develop stomach cancer.

- **Helicobacter Pylori Infection:** This infection is caused by a bacterium called Helicobacter pylori (H pylori). This bacteria increases the risk for developing stomach cancer. A long-term infection with H pylori can lead to another medical condition called chronic atrophic gastritis which causes the inner layer of the stomach to become swollen (a possible pre-cancerous changes of the stomach lining) and progresses until the glandular tissues are destroyed.

- **Pernicious Anemia:** The stomach lining contains cells that produce a substance that helps the body absorb vitamin B\textsubscript{12} from food. If these cells do not produce enough of this substance, it results in a B\textsubscript{12} deficit that leads to anemia. Patients with pernicious anemia are at a slightly higher risk for developing stomach cancer.

- **Menetrier Disease (Hypertrophic Gastropathy):** This is a rare disease associated with low acid production and changes in the stomach lining.

- **Hereditary Nonpolyposis Colorectal Cancer and Familial Adenomatous Polyposis:** These two inherited genetic disorders slightly increase the risk of developing stomach cancer for those family members who inherited either genetic disorder.

- **Infectious Mononucleosis:** This medical condition is caused by a virus called Epstein-Bar. This virus is linked to several forms of lymphoma and it was also found in about 5-10 percent of stomach cancer patients. Stomach cancer cause by mononucleosis is a less aggressive form of cancer with a slow growing process and a low tendency to spread.
• **Intestinal Metaplasia**: This is a medical condition where the normal lining of the stomach is replaced with cells similar to intestinal cells. Intestinal metaplasia can also increase the risk of developing stomach cancer.

• **Stomach Polyps**: Polyps are non-cancerous growths that develop on the lining of the stomach and if left untreated, can eventually become cancerous.

• **Peutz-Jeghers Syndrome**: This disorder is a rare medical condition (that can be inherited or occur spontaneously) characterized by a growth of polyps in the digestive tract. The digestive tract is a hollow tube divided into four segments which include: the esophagus, stomach, small intestine, and colon (large intestine).

11) **Genetic mutations**: People that carry a mutation of the breast cancer genes (known as BRCA₁ and BRCA₂); have a higher risk for developing stomach cancer.

12) **Geographic location**: Stomach cancer is more common in Japan, China, Southern and Eastern Europe, and South and Central America. It is less common in Northern and Western Africa, Melanesia, South Central Asia, and North America.

1.1.6 **Treatment Of Gastric Cancer**

Stomach cancer treatment plans vary from patient to patient and depend on the stage and location of the cancer, the patient's age, and general health state. The three main treatment options for stomach cancer are surgery, chemotherapy and radiotherapy\(^{(14, 15)}\).

**Surgery** - Surgery is a common treatment option for gastric cancer and is either curative or palliative. As a curative treatment, the surgery is performed when the tumor is confined to a certain area, has not spread to adjacent organs and structures, and the patient's health state is good. As a palliative treatment, surgery is performed to remove the tumor in order to prevent tumor bleeding or a stomach blockage. There are six types of surgeries performed in gastric cancer patients. The medical decision for the type of
surgery performed is based on such factors as: 1) the cancer stage, 2) the tumor location, 3) the growth pattern identified on the biopsy tissue sample, and 4) the expected location of lymph nodes affected. The six types of surgeries include:

1. **Endoscopic Mucosal Resection**: During this surgical procedure, the tumor is removed with an endoscope. Endoscopic Mucosal Resection is only performed in patients with cancer located in the mucosal layer of the stomach and when there is a low chance for the cancer to spread.

2. **Subtotal Gastrectomy**: This is a surgical procedure where part of the stomach is removed. It is recommended for patients with cancer located in the lower parts of the stomach near the small intestine. Sometimes, during subtotal gastrectomy part of the small intestine is removed along with those parts of the stomach affected by cancer. Also, the spleen, which filters the blood and removes old blood cells, is removed as well.

3. **Total Gastrectomy**: This is a surgical procedure where the entire stomach is removed. During this procedure, part of the small intestine, other tissues near the tumor and the spleen may also be removed. A total gastrectomy is recommended when the cancer is located in the upper and middle part of the stomach. During the surgery, the doctor will try to create a new stomach using part of the small intestine. The small intestine is then attached to the esophagus which allows the patient to continue eating after surgery. The disadvantage of the "new stomach" is that the patient gets full fast. Therefore, food has to be eaten in small amounts at a time and many times per day.

4. **Endoluminal Stent Placement**: This medical procedure is recommended when the tumor blocks the opening of the stomach and the complete removal of the stomach cannot be performed. During this procedure, the doctor inserts a stent (a
thin, flexible tube) to keep the entrance of the stomach opened, allowing the patient to eat normally.

5. **Endoscopic Laser Surgery:** This surgical procedure uses an endoscope with a laser attached to remove the tumor. Endoscopic laser surgery can also be used when the tumor is located at the entrance of the stomach and blocks the flow of food.

6. **Electrocautery:** This is a medical procedure that uses a cautery to remove lesions or control bleeding. The cautery is a medical instrument which transmits electric current to create heat.

**Chemotherapy** - Chemotherapy is another treatment option for gastric cancer. Chemotherapy uses anti-cancer drugs to stop the growth of the cancer cells by either killing them or stopping the division process. Chemotherapy drugs are sometimes feared because of a patient's concern about toxic effects. Their role is to slow and hopefully halt the growth and spread of a cancer. There are three goals associated with the use of the most commonly-used anticancer agents.

1. Damage the DNA of the affected cancer cells.

2. Inhibit the synthesis of new DNA strands to stop the cell from replicating, because the replication of the cell is what allows the tumor to grow.

3. Stop mitosis or the actual splitting of the original cell into two new cells. Stopping mitosis stops cell division (replication) of the cancer and may ultimately halt the progression of the cancer.

Gastric cancer patients receive chemotherapy: 1) as the primary treatment (when the cancer spread to distant organs), 2) in addition to surgery (as an adjuvant treatment - to enhance the results of the surgery by destroying possible cancerous cells that could have been left behind and to reduce the risk of cancer relapse), 3) before surgery (as a
neoadjuvant treatment - to reduce the size of the tumor) and 4) with radiotherapy (it delays the cancer recurrence and extends the life span of the patient). These drugs enter the bloodstream and reach all areas of the body. As like all treatment options, chemotherapy has side effects which include:

- Nausea and vomiting
- Mouth sore (chemotherapy can cause sore sensations in your mouth and small ulcers can develop)
- Hair loss (chemotherapy does not only attach and kill cancerous cells, it also kills healthy cells causing hair to fall out)
- Bruising and bleeding
- Anemia
- Low resistance to infections
- Tiredness
- Early menopause (for female patients)

**Radiotherapy** - Radiotherapy or radiation therapy is another treatment option for cancer. Radiotherapy uses high-energy rays or particles to destroy cancerous cells. However, this therapy is not commonly used to treat gastric cancer because the stomach is located in the abdominal cavity near major organs and radiotherapy cannot be administrated without affecting them. Radiotherapy can be prescribed for those patients where the cancer spreads beyond the stomach and causes pain. Small doses of radiation beam can relieve the pain. Radiation therapy can be administrated in combination with chemotherapy in a treatment known as chemo-radiotherapy or after surgery to destroy cancer cells that remained after surgery. There are two types of radiation therapy:

1. **External radiation therapy** uses an external device (linear accelerator) to generate high-energy rays that focuses on the targeted area.
2. Internal radiation therapy uses small radioactive pellets (needles, seed, wires or catheters) implanted into affected area.

The side effects of this treatment are nausea, vomiting, diarrhea, fatigue, and mild skin discomfort.

1.1.7 Medical Tests & Diagnosis

**Anamnesis** (detailed medical review of past health state): One of the first steps in establishing a cancer diagnosis is a detailed and complex medical review of the patient's past health problems and general health state, followed by a detailed interview focused on displayed symptoms and gastric cancer risk factors:

**Physical Examination:** The role of a physical examination is to confirm the general health state and to identify possible signs of the cancer. The doctor will also look for any abnormal changes on the abdominal area.

**Blood Tests:** There are three blood tests used in the diagnoses process of gastric cancer: 1). β-hCG assay, 2). CA-125 assay, and 3) CEA assay. These three substances are produced both by cancerous and normal cells. When the level of these substances is higher than the normal limits, it can be a sign of gastric cancer.

**Imaging Tests**

- **Barium Upper Gastrointestinal Radiography:** This test is performed in order to visualize any abnormalities or changes that occurred in the normal outlook of the stomach, esophagus and the first part of the small intestine lining (called Upper GI). In order to perform this image test, the patient will swallow a barium-contrasting substance. Barium is a liquid that coats the lining of the esophagus, stomach and small intestine making it more visible for the x-ray device. Prior to this test, the patient is asked to not eat and drink any liquid for at least 6 hours.
before the test. Once swallowed, the barium will start working in less than one hour. Also, one of the main side effects of this test is: constipation and pale stools for few days after the test.

- **Computed Tomography (CT scan):** This image test is similar with an x-ray test and creates a detailed cross-sectional image of the body. A CT scan is usually performed in two steps. First, the patient's targeted area will be scanned. Second, the patient receives a contrast agent through IV which allows the cancer to be better visualized and then the targeted area is scanned one more time. Both sets of pictures are compared. A CT scan is an efficient test in the diagnoses process because it offers a clear image of the stomach and confirms the exact location of the cancer. Also, a CT scan can show if the cancer has spread to adjacent organs or structures, or distal organs. This image test can help establishing a treatment plan.

- **Positron Emission Tomography (PET):** This is another image test used successfully in diagnosing stomach cancer. Positron Emission Tomography uses radioactive glucose to locate cancer. This glucose contains a radioactive atom that is absorbed by the cancerous cells. The radioactivity is then detected by a special camera. A PET scan is efficient in determining whether or not the cancer has spread beyond the stomach.

- **Magnetic Resonance Imagining (MRI):** This image test uses radio waves and strong magnets to reveal a complete image of the body targeted area. The energy from the radiowaves is absorbed by the tissues and then revealed into a recognizable pattern on a special monitor.
Endoscopy Procedures

- **Upper Endoscopy**: This type of endoscopy is performed to reveal the esophagus, stomach, and the first part of the small intestine (Upper GI). Following sedation of the patient, the doctor uses a thin, flexible, lighted tube which is inserted through the patient's throat into the digestive tract. The endoscope allows the doctor to see inside the esophagus, stomach and small intestine and examine the possible abnormalities and changes that occurred. If needed, tissue samples are taken during the endoscopy for microscopic examination. Before an endoscopy, the patient is not allowed to eat and drink for several hours. The main side effect of this procedure is a discomfort sensation in the throat.

- **Endoscopic Ultrasound (EUS)**: This procedure offers an accurate identification of the cancer stage by combining two classic tests: endoscopy and ultrasound. The doctor inserts a transducer type endoscope via the throat in order to "see" inside the patient's stomach. This type of endoscope works as an ultrasound device that sends out high-frequency sound waves to create an image of the stomach. The advantage of this procedure is that the transducer is placed directly near the stomach walls allowing the ultrasound to precisely determine how far the tumor has invaded the stomach walls and how many adjacent lymph nodes are affected. Before this procedure, the patient is asked to not eat and drink for at least four hours.

- **Laparoscopy**: This is a surgical procedure used to check the health state of organs within the abdominal cavity. This procedure uses a thin tube, called a laparoscope, which is inserted through a small incision into the patient's abdomen. The doctor can closely examine the stomach and adjacent lymph nodes for signs of cancer. This procedure can be performed in combination with ultrasound techniques in order to obtain a better image of the stomach and
INTRODUCTION

surrounding areas. If needed, tissue samples can be taken and examined under microscope.

1.2 COMBINATION CHEMOTHERAPY

Combination of active agents has been used since the late 1970’s, aiming to improve the results of single agent chemotherapy. 5-FU has almost been universally used as the basis in the designing of combination treatment. Advances in basic research resulted in better understanding of the mechanism of action of many chemotherapeutic agents, including 5-FU, the main drug used in advanced gastric cancer. In vitro studies have shown that methotrexate can enhance the activity of 5-FU by blocking the pyrimidine salvage pathway, thus leading the increased intracellular phosphoribosyl pyrophosphate. This shifts 5-Fu into the RNA pathway, increasing destruction of cancer cells. Based on these data several second generation regimens were developed in the late 1980s. FAMTX (5-FU, adriamycin, and high dose methotrexate) showed response rates ranging from 33-50% in phase II studies. The two most effective regimens FAMTX and EAP were also directly compared in a prospective randomized study. FAMTX showed higher activity with significantly lower toxicity. So the authors concluded that FAMTX should be the standard chemotherapy in advanced gastric cancer. Another one ECF was compared with FAMTX in a recent randomized trial which suggested that both regimens are highly cost effective. The uses of second generation regimens which combine 5-FU with other agents that modulate the activity of 5-FU have improved response rates in inoperable gastric cancer and in certain cases have resulted in a small increase in survival. FAMTX has shown considerable efficacy in advanced gastric cancer (16, 17, 18, 19, 20, 21, 22).

1.3 STOMACH OR SITE SPECIFIC DRUG THERAPY

It is one that is designed to treat only the cancer cells and minimize damage to normal cells, healthy cells. Cancer treatments that deliver drug at tumor site may offer the advantage of reduced treatment related side effects and improved outcomes. The
majority of drugs used in the cancer treatments are administered systemically, orally, or locoregionally. Of these, only locoregional delivery presumes restriction of an administered drug to the site or location of the tumor. Thus because the concentration of antineoplastic agent at the tumor site is enhanced, systemic exposure is avoided or significantly minimized. Consequently it is assumed that the therapeutic benefits as well as therapeutic window of the drug are improved upon. The basic principle of regional administration of the antineoplastic agent is to deliver a higher concentration of the agent to the tumor present within a particular region of the body and to expose the tumor to the active drug for longer period of time than are safely possible with systemic administration. In the fight against cancer, new drug delivery systems are attractive to improve drug targeting of tumors (locoregional delivery), maximize drug potency, and minimize systemic toxicity. In the present work a new drug delivery system has been studied comprising Porous Microspheres, i.e. Stomach Specific Floating Drug Delivery System that has bulk density less than gastric fluids and so 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 system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as ‘hydrodynamically balanced systems’ (‘HBS’) since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant (6-8 hours) on the gastric contents without affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents\(^{(23, 24)}\).
1.4 FLOATING DRUG DELIVERY SYSTEM

Floating technology, are low density systems having sufficient buoyancy to float over the gastric contents and remain in the stomach for prolonged period. Unfortunately floating device administered in a single unit form are unreliable in prolonging the GRT owing to their “all or liable emptying process and thus they may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site on GIT.

In contrast multiple unit particulate dosage forms example porous microspheres have the advantages that they pass uniformly through the GIT to avoid the variability’s of gastric emptying and provide an adjustable release, thereby reducing the inter-subject variability in absorption and risk of local irritation than the use of single unit dosage forms\(^{(25, 26)}\).

1.4.1 Porous Microspheres

It is a type of FDSS. Multiple unit dosage forms such as microspheres provide the possibility of achieving long lasting and more reliable release of drugs. The multiple unit dosage forms have a specific surface that is about thousand times greater than the single unit dosage form in equivalent dosage. Conventionally, the microspheres include microparticles, which are substantially spherical and of micron size. In this the drug is dispersed homogeneously in the polymer matrix. The microsphere may have a size range less than 200µm give good retention in the stomach. Gastric retention of porous microspheres is increased because of buoyancy. The demand of microspheres to float in gastric fluid must comply with or any one of the following factors\(^{(27, 28)}\).

- Sufficient structure to form a cohesive gel barrier.
- Overall specific gravity lower than the gastric contents (1.004-1.010).
- Dissolved slowly enough to serve as a drug reservoir.
1.4.2 Drug Candidates For FDDS

A controlled drug delivery system with prolonged residence time in the stomach is of particular interest for drugs that:

i) Are locally active in the stomach,

ii) Have an absorption window in the stomach or in the upper small intestine,

iii) Drugs with narrow window of absorption,

iv) Are unstable in the intestinal or colonic environment, or

v) Exhibit low solubility at high pH values\(^{(29,30)}\).

1.4.3 Drugs Used In the Formulations of Stomach Specific Floating Dosage Forms

- **Floating microspheres** – Aspirin, Griseofulvin, p-nitroaniline, Ibuprofen, Ketoprofen, Piroxicam, Verapamil, Cholestyramine, Theophylline, Nifedipine, Nicardipine, Dipyridamol, Tranilast and Terfinadine.

- **Floating granules** - Diclofenac sodium, Indomethacin and Prednisolone.

- **Films** – Cinnarizine, Albendazole.

- **Floating tablets and Pills** - Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Fluorouracil, Isosorbide mononitrate, Paracetamol, Piretanide, Theophylline, Verapamil hydrochloride, Chlorpheniramine maleate, Aspirin, Calcium Carbonate, Fluorouracil, Prednisolone, Sotalol, pentoxyfilline and Diltiazem HCl.

- **Floating Capsules** - Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L-Dopa, Benserazide, Ursodeoxycholic acid and Pepstatin, and Propranolol\(^{(30)}\).

1.4.4 Polymers And Other Ingredients

Following types of ingredients can be incorporated into HBS dosage form in addition to the drugs:
INTRODUCTION

- **Hydrocolloids (20%-75%)**: They can be synthetics, anionic or non-ionic like hydrophilic gums.
- **Modified cellulose derivatives**: Eg. Acacia, pectin, chitosan, agar, casein, bentonite, veegum, HPMC (K4M, K100M and K15M), Gellan gum (Gelrite®), Sodium CMC, MC, HPC.
- **Inert fatty materials (5%-75%)**: Edible, inert fatty materials having a specific gravity of less than one can be used to decrease the hydrophilic property of formulation and hence increase buoyancy. Eg. Beeswax, fatty acids, long chain fatty alcohols, Gelucires® 39/01 and 43/01.
- **Effervescent agents**: Sodium bicarbonate, citric acid, tartaric acid, Di-SGC (Di-Sodium Glycine Carbonate, CG (Citroglycine)).
- **Release rate accelerants (5%-60%)**: e.g. lactose, mannitol.
- **Release rate retardants (5%-60%)**: eg. Dicalcium phosphate, talc, magnesium stearate.
- **Buoyancy increasing agents (up to 80%)**: eg. Ethyl cellulose.
- **Low density material**: Polypropylene foam powder (Accurel MP 1000®)(31,32).

**1.4.5 Advantages of FDDS**

1. The Floating systems are advantageous for drugs meant for local action in the stomach e.g. antacids.
2. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence FDDS may be useful for the administration of aspirin and other similar drugs.
3. The Floating systems are advantageous for drugs absorbed through the stomach. E.g. Ferrous salts, antacids.
4. Administration of prolong release floating dosage forms, tablet or capsule; will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric
fluid and would be available for absorption in the small intestine only after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine\textsuperscript{(31,32)}.

### 1.4.6 Disadvantages of FDDS

1. Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.

2. These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.

3. Drugs having significant absorption through GI are required\textsuperscript{(31, 32)}.

### 1.4.7 Principal of Floatation

The principle of floatation was first proposed by Archimedes which is popular as the 'eureka' moment. The principle of floatation states that any floating object displaces fluid which is equal to its own weight. This can further be explained as any object, fully or partially immersed in a liquid, is buoyed by a force exerted by fluid equal to its weight\textsuperscript{(33)}.

Principle of Floatation states that whenever an object is placed on the surface of water

1. It will float on the surface if its density is less than water i.e. 1gm/cm\textsuperscript{3}.

2. The object will float just fully immersed if its density is equal to or slightly greater than that of water.

3. The object will sink if its density is greater than water i.e. 1gm/cm\textsuperscript{3}.

### 1.4.8 Classification of FDDS

**Based on the mechanism of buoyancy FDDS can be classified into:**

A. Single Unit Floating Dosage Systems a) Effervescent Systems (Gas-generating Systems) b) Non-effervescent Systems

B. Multiple Unit Floating Dosage Systems
INTRODUCTION

a) Non-effervescent Systems b) Effervescent Systems (Gas-generating Systems)
c) Hollow Microspheres

C. Raft Forming Systems

A. Single Unit Floating Dosage Systems:

a) Effervescent Systems (Gas-generating Systems): These buoyant systems utilize matrices prepared with swellable polymers like HPMC, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach. Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, Carbopol®, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates.

Ozdemir et al (34) prepared floating bilayer tablets with controlled release for furosemide. The low solubility of the drug could be enhanced by using the kneading method, preparing a solid dispersion with β cyclodextrin mixed in a 1:1 ratio. One layer contained the polymers HPMC 4000, HPMC 100, and CMC (for the control of the drug delivery) and the drug. The second layer contained the effervescent mixture of sodium bicarbonate and citric acid. Radiographic studies on 6 healthy male volunteers showed that floating tablets were retained in stomach for 6 hours and further blood analysis studies showed that bioavailability of these tablets was 1.8 times that of the conventional tablets. On measuring the volume of urine the peak diuretic effect seen in the conventional tablets was decreased and prolonged in the case of floating dosage form.

Penners et al (35) prepared an expandable tablet containing mixture of polyvinyl lactams and polyacrylates that swell rapidly in an aqueous environment and thus stays in
stomach over an extended period of time. In addition to this, gas-forming agents were also incorporated so as soon as the gas formed, the density of the system was reduced and thus the system tended to float on the gastric environment.

Talwar et al \(^{36}\) prepared a once-daily formulation for oral administration of ciprofloxacin. The formulation was composed of 69.9% ciprofloxacin base, 0.34% sodium alginate, 1.03% xanthum gum, 13.7% sodium bicarbonate, and 12.1% cross-linked poly vinyl pyrrolidine. The cross linked PVP initially and the gel forming polymers later formed a hydrated gel matrix that entrapped the gas, causing the tablet to float and be retained in the stomach. The hydrated gel matrix created a diffusion path for the drug, resulting in sustained release of the drug.

\textit{b) Non-effervescent Systems:} This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the ‘plug-type systems’ since they have a tendency to remain lodged near the pyloric sphincter. One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Examples of this type of FDDS include colloidal gel barrier, microporous compartment system, alginate beads, and hollow microspheres.

Another type is a Fluid- filled floating chamber which includes incorporation of a gas-filled floatation chamber into a microporous component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an
appropriate specific gravity and an inert behaviour. The device is of swallowable size, remains afloat within the stomach for a prolonged time, and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated.

A newer Self-correcting floatable asymmetric configuration drug delivery system has a 3-layer matrix to control the drug release. This 3-layer principle has been improved by development of an asymmetric configuration drug delivery system in order to modulate the release extent and achieve zero-order release kinetics by initially maintaining a constant area at the diffusing front with subsequent dissolution/erosion toward the completion of the release process.

![Figure 1.2 Gas Filled Floatation Chamber](image)

Figure 1.2 Gas Filled Floatation Chamber

The system was designed in such a manner that it floated to prolong gastric residence time in vivo, resulting in longer total transit time within the gastrointestinal tract environment with maximum absorptive capacity and consequently greater bioavailability. This particular characteristic would be applicable to drugs that have pH-dependent solubility, a narrow window of absorption, and are absorbed by active transport from either the proximal or distal portion of the small intestine.

Yang et al (37) developed a swellable asymmetric triple layer tablet with floating ability to prolong the gastric residence time of triple drug regimen (tetracycline, metronidazole, and clarithromycin) in Helicobacter pylori–associated peptic ulcers using
INTRODUCTION

HPMC and poly (ethylene oxide) (PEO) as the rate-controlling polymeric membrane excipients. The design of the delivery system was based on the swellable asymmetric triple-layer tablet approach. HPMC and poly (ethylene oxide) were the major rate-controlling polymeric excipients. Tetracycline and metronidazole were incorporated into the core layer of the triple-layer matrix for controlled delivery, while bismuth salt was included in one of the outer layers for instant release. The floatation was accomplished by incorporating a gas-generating layer consisting of sodium bicarbonate and calcium carbonate with swelleble polymers. Over 6-8 hours of sustained delivery of tetracycline and metronidazole was achieved with this dosage form which was still floating.

Streubel et al (38) prepared single-unit floating tablets based on polypropylene foam powder (Accurel MP 1000®) and matrix-forming polymer. Highly porous foam powder in matrix tablets provided density much lower than the density of the release medium. It was concluded that varying the ratios of matrix-forming polymers and the foam powder could alter the drug release patterns effectively.

Wu et al (39) prepared floating sustained release tablets of nimodipine by using HPMC and PEG 6000. Prior to formulation of floating tablets, nimodipine was incorporated into poloxamer-188 solid dispersion after which it was directly compressed into floating tablets. It was observed that by increasing the HPMC and decreasing the PEG 6000 content a decline occurred in in-vitro release of nimodipine. Nur and Zhang (40) formulated floating tablets of captopril using HPMC (4000 and 15000 cps) and carbopol. It was concluded that the buoyancy of the tablet is governed by both the swelling of the hydrocolloid particles on the tablet surface when it contacts the gastric fluids and the presence of internal voids in the centre of the tablet (porosity). A prolonged release from these floating tablets was observed as compared with the conventional tablets and a 24-hour controlled release from the dosage form of captopril was achieved.
INTRODUCTION

Single-unit formulations are associated with problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. The main drawback of such system is “all or none” phenomenon. In such cases there is a danger of passing of the dosage form to intestinal part at the time of housekeeper waves. To overcome this difficulty multiple unit dosage forms are designed.

B. Multiple Unit Floating Systems:

In spite of extensive research and development in the area of HBS and other floating tablets, these systems suffer from an important drawback of high variability of gastrointestinal transit time, when orally administered, because of their all-or-none gastric emptying nature. In order to overcome the above problem, multiple unit floating systems were developed, which reduce the intersubject variability in absorption and lower the probability of dose-dumping. Reports have been found on the development of both non-effervescent and effervescent multiple unit systems. Much research has been focused and the scientists are still exploring the field of hollow microspheres, capable of floating on the gastric fluid and having improved gastric retention properties.

a) Non-effervescent Systems: Not much report is found in the literature on non-effervescent multiple unit systems, as compared to the effervescent systems. However, few workers have reported the possibility of developing such system containing indomethacin, using chitosan as the polymeric excipient. A multiple unit HBS containing indomethacin as a model drug prepared by extrusion process is reported. A mixture of drug, chitosan and acetic acid is extruded through a needle, and the extrudate is cut and dried. Chitosan hydrates and floats in the acidic media, and the required drug release could be obtained by modifying the drug-polymer ratio.

b) Effervescent Systems (Gas-generating Systems): Ikura et al (41) reported sustained release floating granules containing tetracycline hydrochloride. The granules are a mixture of drug granulates of two stages A and B, of which A contains 60 parts of
INTRODUCTION

HPMC, 40 parts of polyacrylic acid and 20 parts of drug and B contains 70 parts of sodium bicarbonate and 30 parts of tartaric acid. Sixty parts by weight of granules of stage A and 30 parts by weight of granules of stage B are mixed along with a lubricant and filled into capsule. In dissolution media, the capsule shell dissolves and liberates the granules, which showed a floating time of more than 8 h and sustained drug release of 80% in about 6.5 h. Floating minicapsules of pepstatin having a diameter of 0.1-0.2 mm has been reported by Umezawa\(^{(42)}\). These minicapsules contain a central core and a coating. The central core consists of a granule composed of sodium bicarbonate, lactose and a binder, which is coated with HPMC. Pepstatin is coated on the top of the HPMC layer. The system floats because of the \(\text{CO}_2\) release in gastric fluid and the pepstatin resides in the stomach for prolonged period. Alginates have received much attention in the development of multiple unit systems. Alginates are non-toxic, biodegradable linear copolymers composed of L-glucuronic and L-mannuronic acid residues. A multiple unit system prepared by Iannuccelli et al\(^{(43)}\) comprises of calcium alginate core and calcium alginate/PVA membrane, both separated by an air compartment. In presence of water, the PVA leaches out and increases the membrane permeability, maintaining the integrity of the air compartment. Increase in molecular weight and concentration of PVA, resulted in enhancement of the floating properties of the system. Freeze-drying technique is also reported for the preparation of floating calcium alginate beads. Sodium alginate solution is added drop wise into the aqueous solution of calcium chloride, causing the instant gelation of the droplet surface, due to the formation of calcium alginate. The obtained beads are freeze-dried resulting in a porous structure, which aid in floating. The authors studied the behavior of radiolabeled floating beads and compared with nonfloating beads in human volunteers using gamma scintigraphy. Prolonged gastric residence time of more than 5.5 h was observed for floating beads. The nonfloating beads had a shorter residence time with a mean onset emptying time of 1 h.
Ichikawa et al.\(^{(44)}\) developed a new multiple type of floating dosage system having a pill in the core, composed of effervescent layers and swellable membrane layers coated on sustained release pills (shown in figure 3). The inner layer of effervescent agents containing sodium bicarbonate and tartaric acid was divided into two sub layers to avoid direct contact between the two agents. These sublayers were surrounded by a swellable polymer membrane containing polyvinyl acetate and purified shellac. When this system was immersed in the buffer at 37ºC, it settled down and the solution permeated into the effervescent layer through the outer swellable membrane. CO\(_2\) was generated by the neutralization reaction between the two effervescent agents, producing swollen pills (like balloons) with a density less than 1.0 g/ml.

![Diagram](image.png)

**Figure 1.3** (a) Different layers (i) Semipermeable membrane, (ii) Effervescent layer (iii) Core pill layer (b) Mechanism of floatation via CO\(_2\)

**Hollow Microspheres:** Hollow microspheres are considered as one of the most promising buoyant systems, as they possess the unique advantages of multiple unit systems as well as better floating properties, because of central hollow space inside the microsphere. The general techniques involved in their preparation include simple solvent evaporation, and solvent diffusion and evaporation. The drug release and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers such as polycarbonate, Eudragit\(^{®}\) S and cellulose acetate were used in the preparation of hollow microspheres, and the drug release modulated by optimizing the polymer quantity and the polymer-plasticizer ratio. Sustained release
floating microspheres using polycarbonate were developed by Thanoo et al\textsuperscript{(45)}, employing solvent evaporation technique. Aspirin, griseofulvin and p-nitroaniline were used as model drugs. Dispersed phase containing polycarbonate solution in dichloromethane, and micronized drug, was added to the dispersion medium containing sodium chloride, polyvinyl alcohol and methanol. The dispersion was stirred for 3-4 h to assure the complete solvent evaporation, and the microspheres obtained were filtered, washed with cold water and dried. The spherical and hollow nature of the microspheres was confirmed by scanning electron microscopic studies. The microspheres showed a drug payload of more than 50%, and the amount of drug incorporated is found to influence the particle size distribution and drug release. The larger proportion of bigger particles was seen at high drug loading, which can be attributed to the increased viscosity of the dispersed phase. Kawashima \textit{et al} \textsuperscript{(46)} described hollow microspheres (microballoons) with drug in their outer polymer shells, prepared by a novel emulsion solvent diffusion method. A solution of drug and enteric acrylic polymer (Eudragit \textsuperscript{®} S) in a mixture of ethanol and dichloromethane is added to the aqueous phase containing polyvinyl alcohol (0.75% w/v) and stirred continuously to obtain o/w emulsion. The microspheres obtained are filtered, water washed and dried. The diffusion and evaporation profiles of ethanol and dichloromethane, suggested a rapid diffusion of ethanol from the droplets into the aqueous phase, which might reduce the polymer solubility in the droplet because of insoluble property of Eudragit \textsuperscript{®} S in dichloromethane. Hence, the polymer precipitation occurs instantly at the droplet surface, forming a film-like shell enclosing dichloromethane and drug. The microspheres showed good flow and packing properties, and a floating time of more than 12 h on acidic medium containing surfactant. Joseph \textit{et al} \textsuperscript{(47)} developed a floating dosage form of piroxicam based on hollow polycarbonate microspheres. The microspheres were prepared by the solvent evaporation technique. Encapsulation efficiency of ~95% was achieved. \textit{In vivo} studies were performed in healthy male albino rabbits. Pharmacokinetic analysis was derived
from plasma concentration vs time plot and revealed that the bioavailability from the piroxicam microspheres alone was 1.4 times that of the free drug and 4.8 times that of a dosage form consisting of microspheres plus the loading dose and was capable of sustained delivery of the drug over a prolonged period.

C. Raft Forming Systems:

Raft forming systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders. The mechanism involved in the raft formation includes the formation of viscous cohesive gel in contact with gastric fluids, where in each portion of the liquid swells forming a continuous layer called a raft. This raft floats on gastric fluids because of low bulk density created by the formation of CO\(_2\). Usually, the system contains a gel forming agent and alkaline bicarbonates or carbonates responsible for the formation of CO\(_2\) to make the system less dense and float on the gastric fluids.

1.4.9 Applications of FDDS

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. These are summarized as follows.

Sustained Drug Delivery

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of <1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited.
Recently sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated in vivo. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours)\(^{(48)}\).

Similarly a comparative study \(^{(49)}\) between the Madopar HBS and Madopar standard formulation was done and it was shown that the drug was released up to 8 hours in vitro in the former case and the release was essentially complete in less than 30 minutes in the latter case.

**Site-Specific Drug Delivery**

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, riboflavin and furosemide.

Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets\(^{(50)}\).

A bilayer-floating capsule was developed for local delivery of misoprostol, which is a synthetic analog of prostaglandin E\(_1\) used as a protectant of gastric ulcers caused by administration of NSAIDs. By targeting slow delivery of misoprostol to the stomach, desired therapeutic levels could be achieved and drug waste could be reduced\(^{(51)}\).

**Absorption Enhancement**

Drugs that have poor bioavailability because of site-specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.
A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric-coated LASIX-long product (29.5%)\(^{(50)}\).

Miyazaki\(^{(52)}\) et al conducted pharmacokinetic studies on floating granules of indomethacin prepared with chitosan and compared the peak plasma concentration and AUC with the conventional commercially available capsules. It was concluded that the floating granules prepared with chitosan were superior in terms of decrease in peak plasma concentration and maintenance of drug in plasma.

Ichikawa\(^{(53)}\) et al developed a multiparticulate system that consisted of floating pills of a drug (p- amino benzoic acid) having a limited absorption site in the gastrointestinal tract. It was found to have 1.61 times greater AUC than the control pills.

1.4.10 Evaluation of FDDS

A. For Single Unit Dosage Forms (Eg: tablets)

(i) Floating lag time: It is the time taken by the tablet to emerge onto the surface of dissolution medium and is expressed in seconds or minutes. (ii) In vitro drug release and duration of floating (iii) In vivo evaluation for gastro-retention. This is carried out by means of X-ray or Gamma scintigraphic monitoring of the dosage form transition in the GIT. The tablets are also evaluated for hardness, weight variation, etc\(^{(26, 54)}\).

B. For Multiple Unit Dosage Forms (Eg: microspheres)

Apart from the In vitro release, duration of floating and in vivo gastro-retention tests, the multiple unit dosage forms are also evaluated for: (i) Morphological and dimensional analysis with the aid of scanning electron microscopy (SEM). The size can also be measured using an optical microscope. (ii) % yield of microspheres (iii) Entrapment efficiency (iv) In vitro floating ability (Buoyancy %) (v) Drug-excipient (DE) interactions: This is done using FTIR. Appearance of a new peak, and/or disappearance
of original drug or excipient peak indicate the DE interaction. Apart from the above mentioned evaluation parameters, granules are also evaluated for the effect of ageing with the help of Differential Scanning Calorimeter or Hot stage polarizing microscopy.

Different studies reported in the literature indicate that pharmaceutical dosage forms exhibiting \textit{in vitro} floating behavior show prolonged gastric residence \textit{in vivo}. However, it has to be pointed out that good \textit{in vitro} floating behavior alone is not sufficient proof for efficient gastric retention \textit{in vivo}. The effects of the simultaneous presence of food and of the complex motility of the stomach are difficult to estimate. Obviously, only \textit{in vivo} studies can provide definite proof that prolonged gastric residence is obtained.

1. Measurement of buoyancy capabilities of the FDDS: The floating behavior is evaluated with resultant weight measurements. The experiment is carried out in two different media, deionised water and simulated meal, in order to monitor possible difference. The apparatus and its mechanism are explained earlier in this article. The results showed that higher molecular weight polymers with slower rate of hydration have enhanced floating behavior and it is more in simulated meal medium compared to deionised water.

2. Floating time and dissolution: The test for floating time measurement is usually performed in stimulated gastric fluid or 0.1 mole.lit-1 HCl maintained at 37°C. It is determined by using USP dissolution apparatus containing 900 ml of 0.1 mole litre^{-1} HCl as the dissolution medium at 37°C. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time. Recently in a study more relevant \textit{in vitro} dissolution method to evaluate a floating drug delivery system (for tablet dosage form). A 100-mL glass beaker was modified by adding a side arm at the bottom of the beaker so that the beaker can hold 70 ml of 0.1 mole.lit^{-1} HCl dissolution medium and allow collection of samples. A burette was mounted
above the beaker to deliver the dissolution medium at a flow rate of 2 ml/min to mimic gastric acid secretion rate. The performance of the modified dissolution apparatus was compared with USP Dissolution Apparatus 2 (Paddle). The problem of adherence of the tablet to the shaft of the paddle was observed with the USP dissolution apparatus. The tablet did not stick to the agitating device in the proposed dissolution method. The drug release followed zero-order kinetics in the proposed method. Similarity of dissolution curves was observed between the USP method and the proposed method at 10% difference level ($f_2=57$). The proposed test may show good *in vitro*-in *vivo* correlation since an attempt is made to mimic the *in vivo* conditions such as gastric volume, gastric emptying, and gastric acid secretion rate.

3. Drug release: Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution.

4. Content uniformity, Hardness, Friability (Tablets): The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. The resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The small and portable hardness tester was manufactured and introduced by Monsanto in the Mid 1930s. Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping.

5. Drug loading, drug entrapment efficiency, particle size analysis, surface characterization (for floating microspheres and beads): Drug loading is assessed by crushing accurately weighed sample of beads or microspheres in a mortar and adding to the appropriate dissolution medium which is then centrifuged, filtered
and analyzed by various analytical methods like spectrophotometry. The percentage drug loading is calculated by dividing the amount of drug in the sample by the weight of total beads or microspheres. The particle size and the size distribution of beads or microspheres are determined in the dry state using the optical microscopy method. The external and cross-sectional morphology (surface characterization) is done by scanning electron microscope (SEM).

6. X-Ray/Gamma Scintigraphy: X-Ray/Gamma Scintigraphy is a very popular evaluation parameter for floating dosage forms. It helps to locate dosage form in the g.i.t. and by which one can predict and correlate the gastric emptying time and the passage of dosage form in the GIT. Here the inclusion of a radio-opaque material into a solid dosage form enables it to be visualized by X-rays. Similarly, the inclusion of a γ-emitting radionuclide in a formulation allows indirect external observation using a γ-camera or scintiscanner. In case of γ-scintigraphy, the γ-rays emitted by the radionuclide are focused on a camera, which helps to monitor the location of the dosage form in the GI tract.

7. Pharmacokinetic studies: Pharmacokinetic studies are the integral part of the in vivo studies and several works have been carried out on that. In various studies the pharmacokinetics of verapamil, from the floating pellets containing drug, filled into a capsule, and compared with the conventional verapamil tablets of similar dose (40 mg). The t_{max} and AUC (0-∞) values (3.75 h and 364.65 ng.ml-1h, respectively) for floating pellets were comparatively higher than those obtained for the conventional verapamil tablets. (t_{max} value 1.21 h, and AUC value 224.22 ng.ml-1h). No much difference was found between the C_{max} values of both the formulations, suggesting the improved bioavailability of the floating pellets compared to the conventional tablets. An improvement in bioavailability has also been observed with piroxicam in hollow polycarbonate microspheres administered in rabbits. The microspheres showed about 1.4 times more
bioavailability, and the elimination half-life was increased by about three times than the free drug.

### 1.4.11 Marketed preparation of FDDS

There are several commercial products available based on the research activity of floating drug delivery (Table 1.1)\(^{26, 55}\).

**Table 1.1: Commercial Products Available Based On The Research Activity Of Floating Drug Delivery System.**

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Drugs</th>
<th>Brand Name</th>
<th>Company</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Floating Controlled Release</strong></td>
<td>Levodopa, Benserazide</td>
<td>MODAPAR</td>
<td>Roche Products,</td>
<td>USA</td>
</tr>
<tr>
<td>Floating Capsule</td>
<td>Diazepam</td>
<td>VALRELEASE</td>
<td>Hoffmann-LaRoche</td>
<td>USA</td>
</tr>
<tr>
<td>Effervescent Floating Liquid alginate Preparation</td>
<td>Aluminium hydroxide, Magnesium carbonate</td>
<td>LIQUID GAVISON</td>
<td>Glaxo Smith Kline</td>
<td>INDIA</td>
</tr>
<tr>
<td>Floating Liquid alginate Preparation</td>
<td>Aluminium - Magnesium antacid</td>
<td>TOPALKAN</td>
<td>Pierre Fabre Drug</td>
<td>FRANCE</td>
</tr>
<tr>
<td>Colloidal gel forming FDDS</td>
<td>Ferrous sulphate</td>
<td>CONVIRON</td>
<td>Ranbaxy</td>
<td>INDIA</td>
</tr>
<tr>
<td>Gas-generating floating Tablets</td>
<td>Ciprofloxacin OD</td>
<td>CIFRAN</td>
<td>Ranbaxy</td>
<td>INDIA</td>
</tr>
<tr>
<td>Bilayer floating Capsule</td>
<td>Misoprostal</td>
<td>CYTOTEC</td>
<td>Pharmacia</td>
<td>USA</td>
</tr>
</tbody>
</table>

### 1.4.12 Physiology of Stomach

The Gastrointestinal tract is essentially a tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes the throat (pharynx), esophagus, stomach, small intestine (consisting of the duodenum, jejunum and ileum) and large intestine (consisting of the cecum, appendix, colon and rectum). The wall of the gastrointestinal tract has the same general structure throughout most of its length from the esophagus to the anus, with some local variations for each region. The stomach
is an organ with a capacity for storage and mixing. The antrum region is responsible for the mixing and grinding of gastric contents.

Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50ml and contains a small amount of gastric fluid (pH 1–3) and air. The mucus spreads and covers the mucosal surface of the stomach as well as the rest of the GI tract. The GI tract is in a state of continuous motility consisting of two modes, interdigestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract. The interdigestive motility pattern is commonly called the ‘migrating motor complex’ (‘MMC’) and is organized in cycles of activity and quiescence.

Each cycle lasts 90–120 minutes and consists of four phases. The concentration of the hormone motilin in the blood controls the duration of the phases. In the interdigestive or fasted state, an MMC wave migrates from the stomach down the GI tract every 90–120 minutes.

A full cycle consists of four phases, beginning in the lower esophageal sphincter/ gastric pacemaker, propagating over the whole stomach, the duodenum and jejunum, and finishing at the ileum.

![Figure 1.4 Gastro Intestinal Motility Pattern](image-url)
Phase III is termed the ‘housekeeper wave’ as the powerful contractions in this phase tend to empty the Stomach of its fasting contents and indigestible debris. The administration and subsequent ingestion of food rapidly interrupts the MMC cycle, and the digestive phase is allowed to take place. The upper part of the stomach stores the ingested food initially, where it is compressed gradually by the phasic contractions. The digestive or fed state is observed in response to meal ingestion. It resembles the fasting Phase II and is not cyclical, but continuous, provided that the food remains in the stomach. Large objects are retained by the stomach during the fed pattern but are allowed to pass during Phase III of the interdigestive MMC. It is thought that the sieving efficiency (i.e. the ability of the stomach to grind the food into smaller size) of the stomach is enhanced by the fed pattern or by the presence of food. The fasted-state emptying pattern is independent of the presence of any indigestible solids in the stomach. Patterns of contractions in the stomach occur such that solid food is reduced to particles of less than 1mm diameter that are emptied through the pylorus as a suspension. The duration of the contractions is dependent on the physiochemical characteristics of the ingested meal. Generally, a meal of ~450kcal will interrupt the fasted state motility for about three to four hours. It is reported that the antral contractions reduce the size of food particles to ≤1mm and propel the food through the pylorus. However, it has been shown that ingestible solids ≤7mm can empty from the fed stomach in humans. As described in Table No.1.2

<table>
<thead>
<tr>
<th>Section</th>
<th>Length (m)</th>
<th>Transit time (h)</th>
<th>pH</th>
<th>Microbial count</th>
<th>Absorbing surface area (m²)</th>
<th>Absorption pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>0.2</td>
<td>Variable</td>
<td>1-4</td>
<td>&lt;103</td>
<td>0.1</td>
<td>P, C, A</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>6-10</td>
<td>3 ± 1</td>
<td>5-7.5</td>
<td>103 – 1010</td>
<td>120-200</td>
<td>P, C, A, F, I, E, CM</td>
</tr>
</tbody>
</table>

P – Passive diffusion, C – Aqueous channel transport, A – Active transport, F – Facilitated transport, I – Ion-pair transport, E – Entero-or pinocytosis, CM – Carrier mediated transport
**INTRODUCTION**

*Gastric secretion:* Acid, pepsin, gastrin, mucus and some enzymes about 60 ml with approximately 4 mmol of hydrogen ions per hour.

*Effect of food on Gastric secretion:* About 3 liters of secretions are added to the food. Gastro intestinal transit time is shown in Figure No 1.4.

*Requirements: For Gastric Retention:* Physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease\(^{(26)}\).

**1.5 RESEARCH ENVISAGED**

Stomach cancer is the second worldwide leading cause of cancer related deaths. For the treatment of stomach cancer combination chemotherapy is beneficial.

There are many technologies available to release drug in systemic circulation for the treatment of stomach cancer but much success has not been obtained for the site specific drug delivery. Since no significant scientific study has been done in the management of stomach cancer by floating technology using combination therapy till date, therefore present study has been undertaken to formulate & evaluate the porous microspheres of 5-FU, methotrexate & doxorubicin, a combination chemotherapy for gastric adenocarcinoma.
1.6 PROPOSED METHODOLOGY DURING THE TENURE OF RESEARCH WORK

The main objective of the proposed work is to carry out formulation & characterization of porous microspheres of 5-FluroUracil, Methotrexate & Doxorubicin, a combination chemotherapy for gastric adenocarcinoma.

The research work has been envisaged on the following lines-

1. Preformulation studies
   • Identification of drug – Physical appearance, melting point, UV absorption maxima, comparison of IR spectrum
   • Determination of drug partition
   • Determination of solubility
   • Preparation of calibration curve of drugs
   • Compatibility studies- Drug polymer, drug excipient.

2. Preparation of microspheres by emulsification extraction technique.

3. Optimization of process variables in preparation of microspheres by using $3^2$ full factorial designs
   Independent variables
   • Temperature
   • Stirring speed

   Dependent variables
   • Particle size
   • Percentage drug entrapment
   • Percentage buoyancy

4. Characterization of developed system
   • Micromeritic properties – particle size, true density, tapped density, compressibility index, flow properties.
• Shape & surface morphology.
• Drug content
• Encapsulation efficiency.
• Percentage of buoyancy.
• Fourier transform infrared spectroscopy
• Stability at different gastric pH

5. In-vitro drug release studies
• In vitro drug release
• In vitro cytotoxicity study (IC50)

6. In-vivo studies
• Gamma scintillography.
• Experiment on tumor by using preparation
• Role of porous microspheres in lowering drug induced toxicity

8. Compilation & presentation of data

1.7 LITERATURE SURVEYED
Jones et al (1989) (56) reported that the in vitro release of doxorubicin from biodegradable albumin microspheres into human plasma & sodium chloride 0.9% solution could be sustained for up to 10 days & release rates could be controlled by manipulation of the manufacturing conditions.

Willmott et al (1992) (57) studied the incorporation of 14C-doxorubicin within protease sensitive casein microspheres & from measurement of total drug & ‘free’ drug, suggested that most of the doxorubicin was incorporated via a covalent linkage to the matrix protein. Studies using tumor tissue indicated that antitumor activity was mediated
mainly by the covalently bound doxorubicin & that biodegradation of the microsphere matrix was implicated in drug release & biological disposition & activity.

In a study in rats, Law & Lin (1991) \( ^{(58)} \) investigated the in-vitro & in-vivo release characteristics of methotrexate from microspheres in oil in water emulsions. Rapid & slow biophasic drug release was demonstrated. A similar but slower release rate of methotrexate was observed following the addition of phosphotidylcholine to the emulsions.

Yoon et al (1991) \( ^{(59)} \) investigated & prepared methotrexate-bovine serum albumin conjugates, which may have potential to reduce the toxicity of antineoplastic drugs. Release in-vitro was biphasic & the rate was dependent on the quantity of methotrexate in conjugate & the pH of the release medium. Activity in tissue culture was influenced by a combination of several factors.

Ke W et al (2008) \( ^{(60)} \) reported the enhanced oral bioavailability of doxorubicin in a dendrimer drug delivery system. The doxorubicin-PAMAM complex led to the bioavailability that was more than 200 fold higher than that of the free doxorubicinafter oral administration. These results indicate that PAMAM dendrimer is a promising novel carrier to enhance the oral bioavailability of drug, especially for the p-glycoprotein substrate.

Paharia et al (2007) \( ^{(61)} \) developed eudragit coated pectin microspheres of 5-FU for colon targeting. Results indicated that the microsphere size was low with good drug loading efficiency. No significant swelling was observed with eudragit coated pectin microsphere as compared with pectin microsphere, thus ensuring better resistance of eudragit coated
microsphere in the upper GIT to swelling & preventing subsequent drug release at the target size.

Arhewoh et al (2005)\(^{(62)}\) reviewed the optimizing oral systems for the delivery of therapeutic proteins & peptides. Study concluded that various delivery systems for oral administration of therapeutic substances have been developed for site specific delivery in GIT region.

Chouhan et al (2009)\(^{(63)}\) performed real time in vitro studies of doxorubicin release from PHEMA nanoparticles and they were concluded that polymerization of 2 hydroethyl methacrylate (HEMA) results in the formation of swellable nanoparticles of defined composition PHEMA nanoparticles can potentially be used for the controlled release of the anticancer drug doxorubicin.

Somani et al (2009)\(^{(64)}\) formulated a floating pulsatile drug delivery system based on hollow calcium pectinate beads and concluded that novel hollow calcium pectinate beads beads containing aceclofenac were prepared by a simple ionotropic gelation technique with in situ action of buoyancy imparting agent during formation. Overall, buoyancy provided lag phase in the acidic medium while a pulsatile drug release in alkaline pH that would be useful for rheumatoid and osteoarthritis. This can be extended for time scheduled drug having low solubility, poor or degradation in the lower git.

Dhanraj et al (2005)\(^{(65)}\) studied the active delivery of methotrexate microsphere with mouse monoclonal IgG in tumor induced mice and concluded that methotrexate immuno microsphere was therapeutically efficient in terms of better affinity and binding capacity than methotrexate microspheres and free methotrexate in protecting the mice from carcinoma.
Bromberg et al (2002) \(^{66}\) prepared smart microgel and reported interaction of polyether modified poly (acrylic acid) microgels with antitumor drugs and concluded that microgels that consist of loosely crosslinked poly (acrylic acid) onto which pluronic F127 (EO99, PO67, EO99) or L92 (formula EO8, PO52, EO8) segments are grafted. The microgel based on this is irritatibng in nature.

Pornsak et al (2004) \(^{67}\) investigated morphology and buoyancy of oil entrapped calcium pectinate gel beads and concluded that a new floating system of oil-entrapped calcium pectinate gel beads floated if sufficient amount of oil was used. Scanning electron photomicrographs demonstrated very small pores, ranging between 5 and 40 \(\mu m\), dispersed all over the beads. The type and percentage of oil play an important role in controlling the floating of oil-entrapped CaPG beads. The results suggested that oil-entrapped CaPG beads were promising as a carrier for intragastric floating drug delivery.

Jain et al (2006) \(^{68}\) evaluated porous carrier based floating orlistat microspheres for gastric delivery and concluded that the calcium silicate floating multiparticulate delivery system radiolabelled with 99mTc can be successfully visualized by scintigraphy to establish gastro retentive performance in the rabbit. The results clearly indicated the controlled and sustained release of OT from CS based gastroretentive floating microsphere. Further, the microsphers could also be compressed into tablets filled into capsules or formulated into oral suspension for reconstitution.

Shishu et al (2007) \(^{69}\) formulated multiple-unit floating beads of 5-FU to provide sustained release of drug with a view to provide an effective and safe therapy for stomach cancer with a reduced dose and reduced duration of therapy. The formulation N\(_3\) exhibited the optimum sustained release of 5-FU, with excellent floating properties. Also, in vivo antitumor studies confirmed that the overall rate of tumor incidence and
number of tumors/mouse was less in the animal group treated with FDF of 5-FU than in
the animal group treated with pure 5-FU in the B(a)P-induced tumor model of mice.
Therefore, the floating-type gastroretentive dosage form of 5-FU may be better for
treating gastric tumors.

Kale et al. (2007) (70) produced a multiple unit floating drug delivery system of
piroxicam using eudragit polymer and concluded that hollow microspheres by the
emulsion-solvent diffusion method had excellent buoyancy, good micromeric
properties and in adaptable to any intragastric condition. These microspheres could be
easily handled and can be filled into capsule. Therefore, multiple unit system based on
eudragit microsphere would be of significance as FDDS for sustained drug delivery by
the oral route.

Cheung et al. (2005) (71) reported in vitro efficacy and toxicity of intratumorally delivered
mitomycin C and its combination with doxorubicin using microspheres formulation and
reported that biodegradable sulfopropyl dextran microspheres and their oxidized
products were used to load Dox and MMC, respectively. EMT6 mouse mammary cancer
cells were injected into the hind leg of BALB/c mice. MMC microspheres, alone or
combined with Dox microspheres, were injected i.t. once tumors had reached around 0.3
g. The tumor-plus-leg diameter was measured daily and the delay in time for the tumor
to grow to 1.13 g relative to control (TGD) was employed as an indication of therapeutic
effect. General toxicity was determined by monitoring weight, appearance and behavior
of the mice. Morphology and histology of tumor and heart tissues were also examined.
An average 79% TGD was observed after i.t. injection of MMC microspheres. The i.t.
co-administration of MMC and Dox microspheres resulted in a 185% TGD. The i.t.
injections of the microsphere formulations did not result in visible signs of toxicity in
animals. In contrast, systemic (i.e. i.p.) injections of MMC solutions caused considerable
general toxicity. This study suggests that i.t. delivery of anticancer drugs by polymeric microspheres is an effective way of improving the therapeutic index for cancer chemotherapy of selected solid tumors under special conditions.

Nakagawa et al (2006) \(^{72}\) prepared floating drug delivery system by plasma technique. In this technique compressed tablet is prepared and 5-FU used as core material with outer composed of 68/17/15 weight ratio of povidone, eudragit RL and NaHCo\(_3\). The tablet is irradiated with pulsed plasma irradiation. The plasma heat flux caused the thermal decomposition of NaHCo\(_3\) to generate Co\(_2\) resultant gas were trapped in bulk phase of the outer layer, so that the tablet turned to have lower density than the gastric fluid and tablet remained buoyant in simulated gastric fluid for prolonged period of time. In addition, the release of 5-FU from the tablet is sustained occurrence of plasma induced crosslink reaction on the outer surface of tablet and well controlled reaction also.

Jones et al (2005) \(^{73}\) investigated delivery of doxorubicin and varapamil to drug resistant melanoma cells using microparticulate system and concluded that the use of microparticulate can increase the antitumor concentration within the tumor cells, hence greater cytotoxic effects on the tumor cells exists. Encapsulating a P-glycoprotein inhibitor and antitumor agent simultaneously, may further increase the drug concentration within the cell.

Defail et al (2006) \(^{74}\) studied controlled release of bioactive doxorubicin from microspheres embedded within the gelatin scaffolds and results indicated that the release was controlled by the incorporation of PLGA microspheres into gelatin constructs. A significant difference was seen in the cumulative release over days 5–16 (\(p < 0.05\)). The bioactivity of doxorubicin released from the microspheres and scaffolds was maintained as proven by significant reduction in viable cells after treatment with PLGA
microspheres as well as with the gelatin constructs ($p < 0.001$). The drug-polymer conjugate can be used as a controlled drug delivery system in a biocompatible scaffold that could potentially promote preservation of soft tissue contour.

Esposito et al (2001)\textsuperscript{(75)} formulated pectin based microspheres and studied the influence of experimental parameters and ionic crosslinking on morphological and dimensional characteristics of pectin microspheres. Crosslinking by calcium chloride and the encapsulation of antibiotics (i.e., metronidazole and tetracycline) gave particles morphologically similar to empty particles but with slower swelling kinetic.

Pica et al (2005)\textsuperscript{(76)} developed gelatin methotrexate conjugate microsphere as a potential drug delivery system and reported that gelatin-methotrexate microspheres for intra-tumor administration have possibilities for minimizing systemic toxicities of methotrexate (MTX) and overcoming its resistance. Gelatin-MTX conjugates prepared by a carbodiimide reaction were crosslinked with glutaraldehyde to form microspheres (MTX: gelatin molar ratios of 2:1, 15:1, and 21:1). Microspheres were evaluated under in vitro tumor conditions at pH 6.5 and 37 degrees C with and without Cathepsin B (Cat B). Some microspheres were capped with an ethanolamine/cyanoborohydride procedure. SEM of broken microspheres revealed a hollow shell structure. Superficial Cat B degradation influenced some free MTX release but produced no conjugate fragment release. HPLC measured release of fragments (<10 kDa) was very little and release of free MTX was small. However, higher drug load microspheres released less free MTX than lower drug load, a substantial lag phase of free MTX release from capped microspheres changed to an initial rapid release in uncapped microspheres, and fragments were only released from uncapped microspheres. Opened unstable Schiff base crosslink’s in uncapped microspheres may allow enzyme to produce conjugate fragments not observed in capped microspheres. Free MTX release may occur from dissolved uncrosslinked conjugate within the hollow microspheres. Important relationships and
observations are described that will be useful for gelatin and perhaps other proteinaceous microspheres.

Giovagnoli et al (2006)\(^{(77)}\) prepared large porous biodegradable microsphere by using a simple double emulsion method for capreomycin sulphate pulmonary delivery and suggested that the double emulsion method allowed the preparation of CS loaded large porous microspheres having suitable characteristics to match respirability requirements. The use of RSM helped to establish the conditions to obtain formulations potentially a constant time and cost and material saving.

Gambhire et al (2010)\(^{(78)}\) developed rifampicin nanoparticles by \(3^2\) factorial designs. The in vitro drug release studies indicated that nanoparticles provided sustained delivery for 12 hrs. Hence this investigation demonstrated the potential of the experimental design in understanding the effect of the formula on variables on the quality of rifampicin nanoparticles.

Rudra et al (2010)\(^{(79)}\) prepared doxorubicin loaded phosphotidyl ethanolamine conjugated nanoliposomes and suggested that PE-conjugated nanoliposomes released the drug in a sustained manner were capable of distributing them in variable organs. This may be used for cell/tissue targeting, attaching specific antibodies to PE.

Patel et al (2008)\(^{(80)}\) optimized fast dissolving etoricoxib tablets prepared by sublimation technique concluded that by adapting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts. Sublimation technique would be an effective alternative approach compared with the use of more expensive adjuvant in the formulation of fast dissolving tablets with improved drug interaction.
Patel et al (2006) formulated intragastric floating drug delivery system of cefuroxime axetil and performed in vitro evaluation. By results they concluded that for the development of controlled release dosage form for poorly soluble drug, polymer blends of different viscosity grade of HPMC and presence of surfactant appears necessary, which imparts hydrophilic environment and wettability to molecule of drug leads to more uniform drug release respectively.

Patel et al (2005) demonstrated mucoadhesive glipizide microspheres and concluded that polymer to drug ratio and stirring speed significantly affected the dependent variables. The microspheres of best batch exhibited a high percentage of mucoadhesion of 78% after 1 hr, 75% drug entrapment efficiency and swelling index of 1.42. The t<sub>80</sub> of 476 minutes indicates that the mucoadhesive microspheres of glipizide could sustain the release of the drug for more than 12hrs. The in vivo study demonstrated significant hypoglucemic activity of the glipizide microspheres.

Kalaria et al (2008) designed biodegradable nanoparticles for oral delivery of doxorubicin and investigated in vivo pharmacokinetic and toxicity studies in rats. Results of study concluded that nanoparticles showed promise in improving oral bioavibility of doxorubicin and reduced cardiotoxicity, through tissue distribution of the these particles remained to be investigated. The particle characteristics appear to be ideal for targeting tumors for EPR effect. Further such formulations should allow treatments of new diseases where there is no proper treatment, for example leishmaniasis.

Arora et al (2005) reviewed floating drug delivery systems and concluded that drug absorption in git is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promise to be a potential approach for gastric retention.
Tanwar et al (2006) (28) reviewed floating microspheres. They suggested that gastroretentive floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs. The increasing sophisticated delivery technologies will ensure the development of increasing number of gastroretentive drug delivery systems to optimize the delivery of molecules that exhibit absorption window, low bioavailability and extensive first pass metabolism. The control of gut transit could be the focus of next decades and will provide substantial benefit to patients.

Umamaheshwari et al (2003) (84) prepared floating microspheres bearing acetohydroxamine acid for the treatment of Helicobacter pylori and suggested that the drug and polycarbonate microsphere both showed anti H. pylori activity in vivo, but the required dose of AHA was effectively reduced by a factor of 10 in the case of polycarbonate microspheres.

Soppimath et al (2001) (85) developed hollow microspheres as floating controlled release systems for cardiovascular drugs. The microspheres had smooth surface, free flowing, good packing properties and 80% yield value. The microspheres tended to float over the gastric media for more than 12hrs. The drug loaded in microsphere was in amorphous state as confirmed by DSC. Controlled release obtained for more than 8hrs. The release kinetics followed different transport mechanism depending upon the nature of the drug molecule.

Lee et al (1997) (86) developed oral drug delivery system using floating microspheres and suggested that when a drug had a low solubility in dichloromethane and high solubility in water and mixture of ethanol/isopropranolol, the drug loading efficiency was the lowest.
The release profiles were significantly difficult depending on the solubility of a drug in the release medium and the physicochemical properties of an encapsulated drug.

Yang et al (2004) \(^{(87)}\) prepared microspheres with microballoons inside for floating drug delivery system from xanthum gum, and gelatin by water in oil method, with theophylline as the model drug. The ratio of the two polymers influenced the size distribution, encapsulation efficiency and drug release appreciably. Drug release was in zero order pattern with initial burst due to complexes of polymer with drug.

Soppimath et al (2006) \(^{(88)}\) investigated effect of co excipient on drug release and floating property of nifedipine hollow microspheres. They concluded that microparticles exhibited floating properties on the simulated gastric fluid for more than 12 hrs. Their percentage buoyancy followed the rank order of: blank (no excipient) > dibutyl phthalate > PEG > poly (ε-caprolactone) after 15hrs of floating.

Jain et al (2009) \(^{(89)}\) formulated and evaluated floating microspheres of famotidine in vitro as a gastroretentive dosage form and reported that the size of floating microspheres increased but the release rate of the drug from microspheres coated layer decreased as the polymer concentration increased. No significant effect of the stirring rate during preparation on drug release was observed. In vitro data obtained for floating drug microsphere of FM showed excellent floatability, good buoyancy and prolonged drug release. Microspheres of different size and drug content could be obtained by varying the formulation variables. Diffusion was found to be the main release mechanism.

Havalder et al (2009) \(^{(90)}\) formulated and evaluated floating matrix tablets of atenolol in vitro. They concluded that lesser floating lag time and prolong floating duration can be
achieved by using the polymer. Xanthum gum retarded the release of drug. An inverse correlation between swelling and drug release was observed, it was found that the formulation with maximum swelling indices shared slower release of the drug.

Varahala Setti et al (2009) prepared and evaluated the controlled release tablet of the carvediol and reported that the dissolution from the matrix tablets was spread over more than 24 hrs and dependent on the type of polymer, its concentration and the type of cyclodextrin used. All the matrix tablets prepared using polyethylene oxide shared good controlled release over more than 24hrs. The drug release mechanism from the matrix tablets was found to be quasi Fickian release.

Neetu Gupta et al (2007) investigated the stomach specific drug delivery of 5-FU using alginate beads. Result of the study showed that formulation exhibited the optimum sustained release of 5-FU, with excellent floating properties. Also, in vivo antitumor studies confirmed that the overall rate of tumor incidence & number of tumor was less in the animal group treated with FDF of 5-FU than in the animal group treated with pure 5-FU in the B(a)P induced tumor model of mice.