Introduction

I. INTRODUCTION

With advances in biotechnology, genomics, and combinatorial chemistry, a wide variety of new, more potent and specific therapeutics are being created. Because of common problems such as low solubility, high potency, and/or poor stability of many of these new drugs, the means of drug delivery can impact efficacy and potential for commercialization as much as the nature of the drug itself. Thus, there is a corresponding need for safer and more effective methods and devices for drug delivery. Indeed, drug delivery systems—designed to provide a therapeutic agent in the needed amount, at the right time, to the proper location in the body, in a manner that optimizes efficacy, increases compliance and minimizes side effects—were responsible for $47 billion in sales in 2002, and the drug delivery market is expected to grow to $67 billion by 2006.

Controlled release drug delivery systems are being developed to address many of the difficulties associated with traditional methods of administration. Controlled release drug delivery employs devices—such as polymer-based disks, rods, pellets, or microparticles—that encapsulate drug and release it at controlled rates for relatively long periods of time. Such systems offer several potential advantages over traditional methods of administration.

First, drug release rates can be tailored to the needs of a specific application; for example, providing a constant rate of delivery or pulsatile release. Second, controlled release systems provide protection of drugs, especially proteins that are otherwise rapidly destroyed by the body. Finally, controlled release systems can
increase patient comfort and compliance by replacing frequent (e.g., daily) doses with infrequent (once per month or less) injection. While a variety of devices have been used for controlled release drug delivery, biodegradable polymer microspheres are one of the most common types and hold several advantages.

Microspheres can encapsulate many types of drugs including small molecules, proteins, and nucleic acids and are easily administered through a syringe needle. They are generally biocompatible, can provide high bioavailability, and are capable of sustained release for long periods of time. Several commercial products are based on polymer microspheres.

Disadvantages of microspheres include difficulty of large-scale manufacturing, inactivation of drug during fabrication, and poor control of drug release rates. For example, Nutropin Depot, comprising Genentech’s recombinant human growth hormone (rhGH) encapsulated within poly(d,1-lactide- co-glycolide) (PLG) microspheres using Alkermes’ proprietary ProLease encapsulation technology, was recently pulled from the market because manufacturing and production costs were too high.

Microsphere drug delivery systems have been fabricated by a variety of techniques including combinations of phase separation or precipitation (Young, 1999), emulsion/solvent evaporation [11, 43, 102, 117, 164, 186, 192], and/or spraying methods [58, 72, 126, 140, 183]. Variations of the fabrication parameters generally allow control of the particle size and size distribution. Drugs may be incorporated into the particles in several different ways depending on the properties of the drug. Hydrophobic therapeutics may be co-dissolved with the polymer in a solvent.
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such as methylene chloride or ethyl acetate. Hydrophilic therapeutics, including proteins, may be suspended in the organic phase as a finely ground dry powder. Alternatively, an aqueous solution of a hydrophilic therapeutic may be mixed with the organic polymer solution to form a water-in-oil emulsion. The emulsion-solvent extraction/evaporation methods are most commonly used, especially at the lab scale. In these processes, a solution containing the polymer (and possibly the drug to be encapsulated) is emulsified in a non-solvent phase (the continuous phase) containing a stabilizer. The emulsion can be prepared with any of a variety of physical methods including homogenization and sonication. The components are chosen such that the solvent is slightly soluble in the non-solvent. For example, to produce microspheres of PLG or polyanhydrides, common solvents are methylene chloride and ethyl acetate used in conjunction with an aqueous continuous phase containing poly(vinyl alcohol) (PVA) as a stabilizer [49]. After emulsification, the solvent is extracted into the continuous phase and allowed to evaporate. At the same time, the non-solvent may penetrate into the polymer rich droplets. Due to loss of solvent, the dispersed phase is enriched in polymer until the droplets “harden” to become particles. The microspheres may then be filtered, washed, and lyophilized.

There are several disadvantages of the emulsion solvent-extraction/evaporation techniques that have limited their application. Because these methods are inherently batch operations, scale up of the processes is difficult and large-scale production can be costly. Another critical problem is that size distributions of particles are generally reproducible but non-uniform. Standard deviations of the distribution equal to 50% of the average size are not uncommon. Since the size of the
spheres directly affects the drug release rate and syringability, it is important that size distributions be relatively narrow. In addition, as described above the presence of organic solvents and aqueous-organic interfaces may have adverse effects on encapsulated drugs [62, 147] decreasing or even eliminating bioactivity. Organic solvents also may be very difficult to remove completely. Since many of the commonly used organic solvents (e.g., methylene chloride) are toxic, the concentration of residual solvent in the microsphere must be tightly regulated.

1.1 ORAL DRUG DELIVERY¹:

Oral drug delivery has been known for decades as the most widely used route of administration among all the routes. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief. Pharmaceutical product designed for oral delivery which are currently available in the market mostly immediate-release or conventional release, which maintains the drug concentration within the therapeutically effective range only, when administered several times a day. This results in a significant fluctuation in the drug level.

Recently, several technical advancements have led to the development of several novel drug delivery systems (NDDS) that could revolutionize method of medication and provide a number of therapeutic benefits. The most important objective of these New Drug Delivery Systems are it would be single dose, the duration of treatment, which releases the active ingredient
over an extended period of time. Second, it should deliver the active entity directly to the site of action, thus minimizing or eliminating side effects. Sustain-release formulation simply prolong the release and hence plasma drug level maintained for an extended period of time, not necessarily at a predetermined rate. These makes oral controlled release are much important, which provides a complete and controlled release of drug throughout the GI tract.

1.2 ORAL CONTROLLED DRUG DELIVERY SYSTEM$^{1-2}$:

The term oral controlled release implies a system that provides continuous delivery of drug for a predetermined period in a predictable and reproducible manner with increased the bioavailability. It include the system are provides control over movement of dosage from through the GI tract. Increased bioavailability of CDDS excluded by several physiological difficulties and highly variable nature of gastric emptying process, it turns to unpredictable and reduce bioavailability.

Most limiting biological factor in development of once daily oral controlled release is the transit time of dosage form through the GI tract.

The Digestive System breaks down and absorbs food. When food is eaten, it is not in a form the body can use. It must be changed for the body to absorb it into the blood and carry it to cells. Digestion is how food and drink are broken down into nutrients the body needs to supply energy and to build and maintain its cells.
The digestive tract is the mouth, the esophagus, the stomach, the small intestine, the large intestine (colon), the rectum, and the anus. Figure 1 is a diagram of the digestive tract.

**Figure 1: Shows the Digestive tract**

**The Mouth**

The mouth is the beginning of the digestive tract. Salivary glands in the mouth start digestion. Saliva has enzymes that begin to digest the starch in food. Chewing breaks food into smaller pieces and mixes it with saliva.
The Esophagus

The esophagus is found in the throat near the trachea (windpipe). It receives food from your mouth when you swallow. Swallowing is voluntary, but after food is swallowed smooth muscles push it down esophagus to the stomach using peristalsis. Peristalsis is shown in Figure 2. At the entry to the stomach, a ring of muscle relaxes to allow food to pass through.

![Figure 2: Shows the Peristalsis movement](image)

The Stomach

The stomach is muscular sac with three jobs. It stores food and liquids. It makes strong acids and mixes them with the stored food and liquids. Glands in the stomach lining make stomach acids. These glands also make an enzyme to digest protein. The stomach has a thick layer of mucous to stop the acids
from dissolving the tissue of the stomach itself. After mixing food and acids, the stomach slowly empties itself into the small intestine.

Different foods spend different lengths of time in the stomach. **Carbohydrates** pass through the stomach quickly. **Proteins** stay in the stomach longer. Fats stay in the longest.

**The Small Intestine**

The small intestine is approximately 22 feet long and has three sections:

- The duodenum
- The jejunum
- The ileum

Contents of the stomach move into the first part of the small intestine called the duodenum. In this section of the small intestine, food mixes with enzymes from the pancreas and the liver.

The pancreas makes an enzyme to break down carbohydrates, fats, and proteins. It also makes insulin, which goes into the blood. Insulin regulates sugar in the blood. For more information about the pancreas, see the Endocrine System.

The liver produces bile. It stores bile in the gallbladder. During digestion, bile ducts in the gallbladder release bile to mix with fats. Bile dissolves fat. After fat dissolves, enzymes from the pancreas and the lining of the small intestine digest it. The liver builds helpful chemicals needed by the body from raw materials absorbed
by the small intestine. The liver detoxifies harmful chemicals and drugs and eliminates them from the body.

The walls of the small intestine produce digestive enzymes that work with the pancreas and liver.

In the jejunum and ileum, nutrients are absorbed into the blood and carried to cells. To learn more about the blood, see the Circulatory System.

Undigested parts of food and dead cells shed from the mucosa are pushed into the large intestine, also called the colon.

**The Large Intestine (Colon)**

The colon connects the small intestine to the rectum. It is about six feet long.

The large intestine has five sections:

- The ceacum
- The ascending (right) colon
- The transverse (across) colon
- The descending (left) colon
- The sigmoid colon

The appendix attaches to the **ceacum**. **Figure 3** is a diagram of the large intestine (colon).
Figure 3: Shows the Large Intestine (Colon).

Left over waste from the small intestine passes into the large intestine (colon) by peristalsis. It enters as a liquid and leaves as a solid. As waste passes through the colon, water is removed. Waste (stool) is stored in the sigmoid colon and empties into the rectum once or twice a day. It normally takes about 36 hours for waste to move through the colon.

Waste is mostly food bits and bacteria. Bacteria in the colon do several jobs. They build some vitamins. They break down food waste. They also protect against harmful bacteria.
The Rectum

The rectum gets its name from the Latin work for "straight". It is eight inches long and connects the colon to the anus. The rectum receives stool from the colon. When anything (gas or stool) comes into the rectum, nerves send a message to the brain. The brain decides if the rectal contents can be released or not. If they can, the sphincters relax and the rectum releases its contents. If the contents cannot be released, the sphincter contracts. The sensation temporarily goes away.

The Anus

The anus is the end of the digestive tract. It is two inches long. It contains the pelvic floor muscles and the two anal sphincters (internal and external). There are special nerves in the upper anus that can tell if the contents are liquid, gas, or solid. The sphincter muscles allow control of stool. The pelvic floor muscles stop stool from coming out when it is not supposed to. The internal sphincter is always tight and keeps stool from coming out when we are asleep or unaware of its presence. When we feel the need to go to the bathroom, the external sphincter holds the stool until reaching a toilet. Then it relaxes.

1.3 ANATOMY AND PHYSIOLOGY OF STOMACH

Stomach is an organ with capacity for storage and mixing. It is located just below the diaphragm in the epigastric and left hydrochondriac region of the abdomen.
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The stomach is anatomically divided into three parts:

1. Fundus.
2. Body.
3. Pylorus (or antrum).

Figure 4: Shows anatomy of Stomach

Stomach made up of fundus and body regions. They are capable of displaying a large expansion to accommodate food without much increase in intragastric pressure. Stomach lining is devoid of villi and it consists of considerable number of gastric pits that contribute to storage capacity of the stomach. Antrum region is responsible for the mixing and grinding of gastric content. There are two main secretion mucus and acid, produced by specialized cell in stomach lining. Mucus is secreted by goblet cells and gastric acid by parietal cells (oxyntic) The Mucus spread and cover the rest.
of GI tract. Under fasting condition the stomach is a collapsed bag with a residual volume of 50 ml and contains a small amount of gastric fluid (pH 1-3) and air.

**Physiological condition:**

At the physiological conditions, the gastric absorption of the most drugs is insignificant, because of its limited surface area, (0.1-0.2 m²) thick layer of mucous coating, the lack of villi on the mucosal surface, and the short residence time. Small intestine is major site of absorption of most of the drug due to its large surface area. It contain Kerckring fold, which possess finger like projections called as villi which increase the surface area 30 times. Its pH range is 5-7.5.

<table>
<thead>
<tr>
<th>pH Range</th>
</tr>
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<tbody>
<tr>
<td>Stomach</td>
</tr>
<tr>
<td>Small intestine</td>
</tr>
<tr>
<td>Large intestine</td>
</tr>
<tr>
<td>Rectum</td>
</tr>
</tbody>
</table>

*Table No. 1: Shows different pH range*
1.4 GASTRIC EMPTYING²⁻³:

The passage from stomach to the small intestine, called as gastric emptying. Delayed gastric emptying is recommended in particular where:

- Drugs are absorbed from the proximal part of the small intestine e.g. vitaminB2 and vitamin C.

- The drug dissolves slowly e.g. griseofulvin.

- The food promotes drug dissolution and absorption e.g. griseofulvin.

Gastric emptying process occurs in both fasting and fed states; however, the pattern of motility differs like in the fasted state, it is characterized by an interdigestive series of electrical events in a cycle manner both through the stomach and small intestine every 2-3 hours. This activity is called the interdigestive myoelectric cycle or migrating myoelectric complex (MMC), which is often divided into four consecutive phase.

Phase I (basal phase) : Period of no contraction lasting from 40 to 60 minutes.

Phase II (Preburst phase) : Period in intermittent contraction and of similar duration for 60 minutes.

Phase III (burst phase) : Period of regular contraction at the maximal frequency lasting from 4 to 6 minutes.
Phase IV: Period of transition between Phase III and Phase I and lasts from 0 to 5 minutes.

Phase III has a housekeeping role and serves to clear all indigestible materials from the stomach and the small intestine. A complete cycle of these four phases has an average duration of 90 to 120 minutes.

After the ingestion of a meal, contraction pattern changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contraction as in phase II of fasted state. These contractions result in reducing the size of food particles (less than 1mm), which are propelled towards the pylorus in a suspension form. During the fed state, onset of MMC is delayed resulting in slow down of gastric emptying rate.

- **Fasted state:**

  Indigestible solid, which include the most solid dosage form, emptying from the stomach as the function of their size. Smaller dosage form less than 1mm can empty with liquid, especially highly viscous liquid. Size of solid is 2mm or more, can stay in the fasted stomach from 0-120 minutes.

  Intestinal transit: Flow of material is faster during phase II and III and no effect during phase I because contraction is minimal; there is little or no movement of content through the intestine. Transit of solid through small
intestine is variable because motor activity may not be sufficiently strong to move the solid particle.

- **Fed state:**

  Liquid emptying faster, compared with solid. Solid are not emptying in fed state unless they have been ground to particle size of 2mm or less. Multi unit dosage form, however will disperse and empty with food and thus achieve a considerable degree of distribution. Total time for gastric emptying varies from 2 to 6 hours. Intestinal transit time for both liquid and solid are around 3-4 hour, in both fasted and fed state.

  Gastric emptying process is variable in nature, it leads unpredictable and reduced bioavailability of dosage form. Most limiting biological factor in development of once daily oral controlled release is the transit time of dosage from through the GI tract.

**1.5 GASTRO-RETENTATIVE DOSAGE FORM**

One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), by using gastro-retentive dosage forms (GRDFs). GRDFs can remain in the gastric region for several hours and hence prolong the gastric residence time of drug. GRDFs offers several advantages over immediate release dosage form, including the minimization of fluctuations in drug concentration in plasma, and at the site of action over prolonged periods of
time, resulting in optimized therapeutic efficiencies and reduce the side effect, reduction of total dose administered, (while providing similar therapeutic effect) and reduction of administration frequency, leading to improved patient compliances.

1.6 FACTORS AFFECTING GASTRIC RETENTION⁶⁻⁹ :

There are several factors that can affect gastric retention of an oral dosage form. These factors are as follows.

1.6.1 Density :

If formulation having density of less than of the gastric fluids 1.004gm/cm³ it can easily float, more than 3gm/cm³, such system retain in the stomach.

1.6.2 Size :

Dosage form units with a diameter of less than 7.5 mm are reported to have an increased GRT compared with those with a diameter of 9.9 mm.

1.6.3 Shape of Dosage Form :

Ring and Tetrahedron shaped devices with a flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT ≈ 90% to 100% retention at 24 hours compared with other shapes.
1.6.4 Single or Multiple Unit Formulation:

Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances. It permits a larger margin of safety against dosage form failure compared with single unit dosage forms.

1.6.5 Fed or Unfed State:

Under fasting state, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.

1.6.6 Nature of Meal:

Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

1.6.7 Caloric content:

GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
1.6.8 Frequency of feed:

GRT can increase by over 400 minutes when successive meals are given compared with single meals due to the low frequency of MMC.

1.6.9 Gender:

Mean ambulatory GRT in males (3.4 ± 0.6 hours) is less compared with their age and race-matched female counterparts (4.6 ± 1.2 hours), regardless of the weight, height and body surface.

1.6.10 Age:

Elderly people, especially those over 70, have a significantly longer GRT.

1.6.11 Posture:

Gastric emptying is favored while standing and by lying on the right side since the normal curvature of the stomach provides a down hill path where as lying on the left side or in supine position retard it.

1.6.12 Disease States:

Diseases like gastro enteritis, gastric ulcer, pyloric stenosis, diabetes and hypothyroidism retard gastric emptying while partial or total gastrectomy, duodenal ulcer and hyperthyroidism promote it.
1.6.13 Concomitant Drug Administration:

Drugs that retard gastric emptying include poorly soluble antacids (aluminium hydroxide), anticholinergics (atropine, propantheline), narcotic or analgesia (morphine) and tricyclic antidepressants (imipramine, amitriptyline), metoclopramide, domperidone and cisapride stimulate gastric emptying.

1.7 VARIOUS GASTRO-RETENTIVE DRUG DELIVERY SYSTEM\textsuperscript{6-9}:

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These include:

1.7.1 Bioadhesive delivery system.
1.7.2 Size increasing system.
1.7.3 High density system.
1.7.4 Low density system.

1.7.1 Bioadhesive system:

Bioadhesive system is adhering to mucosal surface of the stomach after the oral administration. This have high turnover rate of gastric mucus and resulting limited retention time. The disadvantage of this system is possibility of esophageal binding.

Chitosan is also proved for its safety via per oral route. Chitosan microsphere gives a targeted delivery in stomach as they have mucoadhesive
property. Chitosan Microspheres (MS) of for intranasal systemic delivery were developed with the aim to avoid gastro-intestinal complications, to improve patient compliance, to use as an alternative therapy to conventional dosage forms, to achieve controlled blood level profiles, and to obtain improved therapeutic efficacy in the treatment of postoperative pain and migraine. Chitosan microspheres can be prepared using the emulsification-cross linking technique & solvent evaporation method.

**Chitosan as a coating material:**

Chitosan has good film forming properties and hence, it is used as a coating material in drug delivery applications. Chitosan-coated microparticles have many advantages such as improvement of drug payloads, bioadhesive property and prolonged drug release properties over the uncoated particles. Chitosan-coated microspheres composed of poly (lactic acid) – poly (caprolactone) blends have been prepared. These microspheres showed good potential for the targeted delivery of antiproliferative agents to treat restenosis. Shu and Zhu have prepared the alginate beads coated with CS by three different methods. The release of brilliant blue was not only affected by CS density on the particle surface, but also on the preparation method and other factors. Chiou et al have used different molecular weight chitosan for coating the microspheres. The initial burst release was observed in the first hour with 50% release of lidocaine. But, 19.2% release occurred at 25th hour.
for the un-coated particles and 14.6% at the 90th hour for the CS-coated microsphere.

1.7.2 Sized increasing drug delivery system or swelling system:

This dosage forms is an initially small size and that once in the stomach significantly increasing its size above the diameter of the pylorus. The expanded state should be achieved rapidly in order to prevent premature emptying through the pylorus. Conversely the system should also guarantee their clearance from the stomach after predetermined time intervals to avoid accumulation upon multiple administrations.

1.7.3 High-density system:

This system accomplished by coating the drug with a heavy inert are material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. These coated pellets which have density greater than that of stomach content (1.004 gm/cm$^3$). This system having density of ~ 3 gm/cm$^3$ is retained in the range of the stomach. This is accomplished by coating the drug with a heavy inert material such as barium sulphate, zinc oxide, titanium dioxide, iron powder etc. The only major drawback with such system that it is technically difficult to manufacture them with a large amount of drug (>50%) and to achieve the required density of 2.4-2.8 gm/cm$^3$. 

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1.7.4 Floating drug delivery system:

The concept of FDDS was described in the literature as early as 1968. Where Davis discovered a method for overcoming the difficult experience by some persons of gagging or choking while swallowing medicinal pills. The another suggested that such difficulty could be overcome by proving pills having a density of less than 1.004gm/cm$^3$ so they float on water surface. The various buoyant preparation include hollow microsphere (microballoons), granules powder, capsule, tablet (pills) laminated films.

1.8 TYPES OF FDDS$^8$-$^{10}$:

Based on the mechanism of buoyancy, two distinctly different types, i.e. non-effervescent and effervescent systems have been utilized in the development of FDDS. The various approaches used in and their mechanism of buoyancy are discussed in the following subsections.

1.8.1 EFFERVESCENT FDDS:

Effervescent system utilize matrices prepared with swellable polymers such as methocel or polysaccharides e.g., chitosan and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified

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hydrocolloid. This produces an upward motion of dosage form and maintain it buoyancy.

1.8.1.1 Multiple-unit oral floating drug delivery system:

Recently a multiple – unit type of floating pill, which generates carbon dioxide gas, has been developed. The system consisted of sustained – release pills as seeds surrounded by double layers.

The inner layer, an effervescent layer containing both sodium bicarbonate and tartaric acid. The outer layer was a swellable membrane layer containing mainly polyvinyl acetate and purified shellac. Moreover, the effervescent layer was divided into two sublayers to avoid direct contact between sodium bicarbonate and tartaric acid. Sodium bicarbonate was contained in the inner sublayer and tartaric acid was in the outer layer. When the formed swollen pills, like balloons, with a density much lower than 1.004 gm/cm³. The reaction was due to carbon dioxide generated by neutralization in the inner effervescent layer with the diffusion of water through the outer swellable membrane layer.
Figure 5: Shows Multiple-unit oral floating drug delivery system

The system was found to float completing within 10 minutes and approximately 80% remained floating over a period of 5 hours irrespective of pH and viscosity of the test medium.

A floating system utilizing ion-exchange resins has been developed. The system consisted of resin beads, which were loaded with bicarbonate and a negatively charged drug that was bound to the resin. The resultant beads were then encapsulated in a semipermeable membrane to overcome rapid loss of carbon dioxide. Upon arrival in the acidic environment of stomach, an exchange of chloride and bicarbonate ion took place, as was expected. As result of this reaction, carbon dioxide was released and trapped in the membrane, thereby carrying beads toward the top of gastric contents and producing a floating layer of resin beads. In contrast, the uncoated beads sank quickly. Radio activity measurement by scintigraphy showed that gastric residence was substantially prolonged, compared with a control, when the
system was given after a light, mainly liquid meal. Furthermore, the system was capable of slow release of drug. A properly which widens the scope of such floating system for SR preparation of drugs possessing negative charge since they can be easily bound to the resin in combination with bicarbonate ions.

Two patents on FDDS issued to the Alza Corporation disclosed drug delivery devices for the controlled and continuous administration of medicinal agents.

1.8.1.2 Inflatable Gastrointestinal Drug Delivery System:

The residence time of the drug delivery device in the stomach can also be sustained by incorporation of an inflatable chamber, which contains a liquid, e.g., ether that gasifies at body temperature to cause the chamber to float in the stomach.

![Diagram of Inflatable Gastrointestinal Drug Delivery System]

**Figure 6: Inflatable gastrointestinal drug delivery system**
1.8.1.3 Intragastric Osmotically Controlled Drug Delivery System:

It is comprised of an osmotic pressure controlled drug delivery and an inflatable floating support in a bioerodible capsule. When the drug delivery device reaches the site of drug administration e.g. the stomach, the capsule quickly disintegrates to release the intragastric osmotically – controlled drug delivery device. The inflatable floating support is made from a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag.

Figure 7: Shows Osmotic Controlled Drug Delivery System

Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multiple unit dosage
forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of gastro-retentive floating microspheres.

1.8.2 NON-EFFERVESCENT FDDS:

Floating microsphere are gastro-retentive delivery systems based on non-effervescent approach. Gastro-retentive floating microspheres are low density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting increased gastric retention with reduced fluctuations in plasma drug concentration. Hollow microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core.

1.8.2.1 Hydrodynamically Balanced Intragastric Delivery System (HBS):

The hydrodynamically balanced gastrointestinal drug delivery systems, in either capsule or tablet form, is designed to prolong GI residence time in an area of the GI tract to maximize drug reaching its absorption site in solution state and hence, ready for absorption. It is prepared by incorporating a high level (20-75% w/w) of one or more gel-forming hydrocolloids e.g. hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and sodium carboxymethylcellulose into the formulation and then compressing these granules into a tablets (or encapsulating into capsules). On
contact with gastric fluid the hydrocolloid in this intragatric floating device start to become hydrated and forms a colloid gel barrier around its surface with thickness growing with time. This gel barrier controls the rate of solvent penetration into the device and the rate of drug release from the device (fig-3). It maintains a bulk density of less than 1 and thus remains buoyant in the gastric fluid inside the stomach for up to 6 hours.

![Diagram of drug release from gelled capsules]

**Figure 8:** Shows Working Principle of Hydro dynamically Balance System

### 1.8.2.2 Bilayer Tablet:

A bilayer tablet can be prepared to contain one immediate - release layer and one sustained - release layer. After the initial dose is delivered by the immediate release layer, the sustained release layer absorbs the gastric fluid and forms a colloidal gel barrier on its surface. This produces a bulk
density less than that of the gastric fluid and remains buoyant in the stomach for extended period of time.

**Figure 9: Shows Bilayer Tablet**

1.8.2.3 Intragastric Floating Gastrointestinal Drug Delivery System:

A gastrointestinal drug delivery system (GIDS) can be made to float in the stomach by incorporating a floatation chamber, which may be a vacuum or filled with a harmless gas.

**Figure 10: Intra Gastic Floating Drug Delivery Devices**
A drug reservoir is encapsulated inside a microporous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the stomach mucosal surface with the undissolved drug.

In the stomach the floatation chamber causes the GIDS to float in the gastric fluids. Fluids enter through the apertures, dissolve the drug, and carry and drug solute out of the drug delivery system for controlled transport to the intestine for absorption.

1.8.2.4 Hollow microsphere$^{2-3}$:

That floats immediately upon contact with gastric fluid and gives promising approaches for increasing the bioavailability of drugs with absorption windows in upper small intestine and stomach. However, immediate floating can only be achieved, when the density of the device is lower than gastric fluid 1.004 gm/cm$^3$.

Floating dosage form available$^3$:

<table>
<thead>
<tr>
<th>Microsphere</th>
<th>Aspirin Griseofulvin and P – nitro aniline  Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granules</td>
<td>Diclofenace sodium, Indomethacin</td>
</tr>
<tr>
<td>Tablets / Pills</td>
<td>Acetaminophen, Acetyl salicylic acid, amoxycillin trihydrate, ampicillin atenolol, diltiazem, etc</td>
</tr>
<tr>
<td>Capsules</td>
<td>chlordiazepoxide, Diazepam Furosemide, Misoprostol,</td>
</tr>
</tbody>
</table>

Table No. 2: Shows Floating dosage form available
Introduction

1.9 ADVANTAGES OF CHITOSAN MICROSPHERE:

- Improves patient compliance by decreasing dosing frequency.
- Better therapeutic effect of short half-life drugs can be achieved.
- Gastric retention time is increased because of buoyancy.
- Drug releases in controlled manner for prolonged period.
- Site-specific drug delivery to stomach can be achieved.
- Enhanced absorption of drugs which solubilizing only in stomach and upper part of intestine.
- Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, desirable plasma drug concentration is maintained by continuous drug release.
- Avoidance of gastric irritation, because of sustained release effect, floatability release of drug through multiparticulate system.
1.10 LIMITATIONS\textsuperscript{3}:

It is not feasible for those drugs that have solubility or stability problems in gastric fluids. Such as nifedipine, which is well absorbed along the entire GI tract and which undergoes significant first-pass metabolism may not be desirable candidates for GRDDS, since the slow gastric emptying may lead to reduce systemic bioavailability of GR DDS for drugs that are irritant to gastric mucosa.

NSAIDs are used to treat pain in a number of medical conditions. They are also used to treat inflammation, which often produces or worsens pain by causing stiffness and swelling. Some NSAIDs are available without a doctor’s prescription (“over the counter” or OTC medications). These include aspirin, low dose (200 mg) ibuprofen (Advil®, Motrin®, Nuprin®, etc), and low dose naproxen (Aleve®, etc). They are safe and effective medications for the vast majority of patients taking them in appropriate doses. Other NSAIDs are only available with a doctor’s prescription.

1. Carefully read all the directions.
2. Follow any advice and/or precautions.
3. Do not take this medicine if you have ever had any unusual or allergic reactions to aspirin, any over the counter NSAIDs or any other medicine used to treat pain, fever, swelling or arthritis.
4. Make sure that the medication is compatible with any other medications you are taking. Check with your healthcare provider or pharmacist if you don’t know.
5. Check with your healthcare provider if you are pregnant, intend to become pregnant or are breast feeding.

6. Notify your healthcare provider if you have any bleeding or blood clotting problems.

7. Consult with your healthcare provider if you have a history of gastrointestinal bleeding or ulcer before taking NSAIDs.

8. Notify your healthcare provider if you have a history of gastrointestinal bleeding or ulcer before taking NSAIDs.

1. Use only as directed by your healthcare provider.

2. Take NSAIDs with food and a full glass of water (8 oz). You may also take them with antacids.

3. Take only for the prescribed time period recommended by your healthcare provider.

4. If you miss a dose, take it as soon as possible with food and water. If it is almost time for the next dose, skip the missed dose and go back to your regular schedule. Do NOT double dose.

1. If you take NSAIDs for prolonged periods (months), make sure you have regular check-ups by your healthcare provider.

2. Notify your healthcare provider if you regularly consume alcoholic beverages. Your medications may need to be modified.

3. Serious side effects resulting in severe and even life-threatening illness (from such problems as bleeding ulcers and others) can occur without warning.
4. Do not take other NSAIDs, including over the counter NSAIDs (Advil, Nuprin, Aleve) and aspirin, with this prescription. Continuing the use of daily single low dose aspirin compounds for prevention of cardiovascular conditions is usually acceptable.

5. NSAIDs can also affect other medical conditions such as high blood pressure, kidney problems, asthma and others. Make sure you have informed your healthcare provider about all your medical problems and all the medications you take (prescription and over the counter, including vitamins and homeopathic compounds) before taking this new medication.

6. Since some NSAIDs can cause drowsiness; make sure you know how you react to the NSAID before operating machinery or other jobs that require you to be alert.

There are a number of mild problems that can be associated with NSAID use. Mild nausea, indigestion or heartburn can be common and are often prevented by taking the medication on a full stomach with plenty of water. Other mild side effects include mild diarrhea and mild lightheadedness and/or drowsiness. These mild side effects will usually go away. However, if they continue or are bothersome, check with your healthcare provider and stop taking the medication. Although rare, severe side effects can occur with NSAID use that affect many different organ systems. You should immediately stop taking the medication and contact your healthcare provider if you notice any of the following:

1. Severe nausea, heartburn or abdominal pain;
2. Bloody or black tarry stools;
3. Vomiting blood or material that looks like coffee grounds;
4. Recurrent nose bleeds or bleeding from the mouth or gums or other unusual bleeding;

5. Easy and severe bruising;

6. Hives or swelling of the face, eyelids, mouth, lips or tongue;

7. Shortness of breath or difficulty breathing;

8. Wheezing;

9. Tightness in the chest or chest pain;

10. Sudden, unexplained weight gain;

11. Sudden decrease in the amount of urine production;

12. Convulsions or seizures;

13. Elevated blood pressure.
<table>
<thead>
<tr>
<th>S.No</th>
<th>Generic Name</th>
<th>Tradename</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Celecoxib</td>
<td>Celebrex</td>
</tr>
<tr>
<td>2</td>
<td>Diclofenac</td>
<td>Cataflam, Voltaren, Arthrotec</td>
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<tr>
<td>3</td>
<td>Fenoprofen</td>
<td>Nalfon, Nalfon 200</td>
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<tr>
<td>4</td>
<td>Ibuprofen</td>
<td>Motrin, Tab-Profen, Vicoprofen</td>
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<td>5</td>
<td>Indomethacin</td>
<td>Indocin, Indocin SR,</td>
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<td>6</td>
<td>Ketoprofen</td>
<td>Indo-Lemmon, Indomethagan</td>
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<td>7</td>
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<td>10</td>
<td>Sulindac</td>
<td>Feldene, Tolectin, Tolectin DS, Tolectin 600</td>
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</table>

Table No. 3: Shows list of NSAID’s drugs