1. Introduction

The oral route of drug administration is the most important method of administering drugs for systemic effects. The parenteral route is not routinely used for self administration of medication. The topical route of administration has only recently been employed to deliver drugs to the body for systemic effects. It is probable that at least 90% of all drugs used to produce systemic effects are administered by the oral route. When a new drug is discovered, one of the first questions a pharmaceutical company asks is whether or not the drug can be effectively administered for its intended effect by the oral route. If it cannot, the drug is primarily relegated to administration in a hospital setting or physician's office. Solid oral dosage forms represent the preferred class of product. The reasons for this preference are well known. [1]

1.1. Problems of conventional drug delivery

An ideal dosage regimen in the drug therapy of any disease is one which immediately attain the desired therapeutic concentration of drug in plasma and maintains it’s constant for the entire duration of treatment. This is possible through the administration of conventional dosage forms in a particular dose and at particular frequency. The frequency of administration or dose interval of any drugs depends upon its half life or mean residence time and its therapeutic index. In most cases, dosing interval is much shorter than the half life of the drug, resulting in number of limitations associated with such a conventional dosage form which are,

I. Poor patient compliance; increased chances of missing the dose of a drug with short half life for which frequent administration is necessary.

II. A typical peak valley plasma concentration time profile is obtained which makes attainment of steady state condition difficult.

III. The unavoidable fluctuation in the concentration may lead to under medication or over medication as the $C_{ss}$ value fall or rise beyond the therapeutic range.

The fluctuating drug level may lead to precipitation of adverse effect especially of a drug with small therapeutic index whenever over medication occurs. [2]
1.2. **Need of non conventional drug delivery system**

To overcome above discussed limitations of conventional dosage forms, it indicates that the need of the development of non conventional dosage forms.

There are two ways to overcome such a situation which are

I. Development of new, better and safer drugs with long half life and large therapeutic indices.

II. Effective and safer use of existing drugs through concepts and techniques of sustained/controlled and targeted drug delivery systems. [2]

Oral controlled/sustained release dosage forms are being developed since past three decades due to their advantages. The design of oral controlled/sustained release drug delivery systems should primarily be aimed at achieving more predictable and increased bioavailability of drugs. [3]

1.3. **Modified Drug Delivery System (MDDS)**

The oral route of drug delivery is typically considered the preferred and most patient-convenient means of drug administration. While significant advances have been made in the development of elegant systems to modify the oral delivery of drugs, the basic approaches have remained unchanged. Modified release formulation technologies offer an effective means to optimize the bioavailability and resulting blood concentration time profile of drugs. [4] Modified release dosage forms are those preparations where the rate and/or place of release of the active substance(s) are different from that of a conventional release dosage form administered by the same route. This deliberate modification is achieved by a special formulation design and/or manufacturing method. [5]

Modified release delivery systems may be divided conveniently into four categories. [6]

a) Delayed release

b) Sustained release
   i) Controlled release
   ii) Extended release

c) Site specific targeting

d) Receptor targeting
a) **Delayed release:**

These systems are those that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release systems include repeat action tablets, capsules and enteric coated tablets where time release were achieved by a barrier coating.

b) **Sustained release**

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time.

i) **Controlled release:**

Controlled release systems also provide a slow release of drug over an extended period of time and can also provide some control, whether this is of a temporal or spatial nature, or both. In other words, the system is successful at maintaining constant drug levels in the target tissue or cells.

ii) **Extended release:**

Pharmaceutical dosage forms that release the drug slower than normal manner at predetermined rate and necessarily reduce the dosage frequency by two folds.

c) **Site specific targeting:** [7]

Site specific targeting systems refer to targeting of a drug directly to a certain biological location adjacent to or in the diseased organ or tissue.

d) **Receptor targeting:**

Receptor targeting systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems satisfy the spatial aspect of drug delivery and are considered to be controlled drug delivery systems.
According to Caremella et al., oral modified release dosage forms can be classified in different ways. One way is to distinguish between single-unit dosage forms such as tablets and capsules and multiparticulate dosage forms such as pellets and beads. [8]

### 1.4. Rational of controlled drug delivery system

The basic rational for sustained/controlled drug delivery system is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and or physiological parameter inherent in a selected route of administration.

i. Reduction in fluctuation of drug blood levels about the mean.

ii. Reduce the dosage frequency.

iii. To improve patients compliance.

iv. To ensure safety and improve efficacy of drugs.

v. More consistent and prolonged therapeutic effect.

vi. Decreased incidence and intensity of adverse effects and toxicity.


viii. A greater selectivity of pharmacological activity.

ix. Delivery of drug at site at predicted time. [3]

### 1.4.1. Approaches of controlled drug delivery system

Commonly two general approaches for the formulation of controlled drug delivery system, which is, [9]

1. Approach based on drug modification
   a) Drug complex
   b) Drug absorbate
   c) Prodrug

2. Approach based on dosage form modification
   a) Matrix formation
   b) Development of barrier mediated model
1.5. Problems associated with CRDF/SRDF

The inability to restrain and confine these systems to selected regions of gastrointestinal tract has been the principle obstacle to the development of oral controlled release system. Various approaches have been tried to overcome such an obstacle. They include the control of gastric residence time (GRT), using gastro retentive drug delivery system (GRDDS) that will provide us with new and important therapeutic options [10].

1.5.1. Single unit Dosage forms

Single unit dosage forms are defined as oral delivery systems that consist of one unit which contains a single dose of the drug and is intended to be administered singularly [11]. Many single unit dosage forms have been developed for the modified release of bioactive materials. The most widely investigated example is the monolithic matrix based tablet [12, 13, 14]. The advantages of this dosage form include high drug loading and the availability of well characterized and cost-effective production methods. Drug release from these systems is controlled by a variety of mechanisms, including drug diffusion, tablet erosion, matrix swelling or a combination of these mechanisms. Film coated and osmogen controlled single unit dosage forms have also been studied for modified release applications [15, 16]. Single unit includes Capsules, Coated tablets, Osmotic pumps, Insoluble matrix tablets, soluble matrix tablets, degradable matrix tablets and ion exchange resins.

1.5.2. Multiple unit dosage forms

The concept of the multiple unit dosage form was introduced in the early 1950s. These solid oral dosage forms consist of a multiplicity of small discrete particulates, which include mini tablets, pellets and granules [17]. These systems provide flexibility during formulation development and gives therapeutic benefits to patients. A significant advantage of multiparticulates is that they can be divided into desired doses without making formulation or process changes. They can also be blended to deliver simultaneously incompatible bioactive agents or particles with different drug release properties. Furthermore, these dosage forms are less susceptible to dose dumping than the reservoir or matrix type, single unit tablet since the drug release profile does not depend on the drug release properties of a single unit [18].
Pellets offer advantages as they constitute multiple unit dosage forms, studies have indicated that they are rapidly and evenly dispersed in the gastrointestinal tract upon oral administration, thus maximizing drug absorption and reducing inter and intra subject variability due to differences in gastric emptying rates [19]. Pellets can be filled into hard gelatin capsules or compressed into tablets, which rapidly disintegrate into multiple units. Multiple units include Pellets, Granules, Microcapsules, and Beads etc.

1.6. **Introduction to Chronopharmaceutics:**

In the field of modified release, matching of drug release to the body’s circadian rhythms have been one of the main strategies involving the selection of a new drug delivery system which increase the efficacy and safety of drugs by proportioning their peak plasma concentrations during the 24 hours in synchrony with biological rhythm. With an increasing number of several diseases showing chronopharmacological variations as well as various drugs showing pharmacokinetic and pharmacodynamic variations, there seems to be an emerging area of pharmaceutics called chronopharmaceutics that release a bioactive reagent at a rhythm that ideally matches the biological requirement of a given disease therapy. The various diseases where this therapy can be used are Allergic rhinitis, Asthma, Rheumatoid arthritis, Osteoarthritis, Peptic ulcer, Hypertension, Angina pectoris, Myocardial infarction, Sudden cardiac death, Stroke, Hypercholesterolemia, Neurological disorders, Cancer, Diabetes etc

All forms of life on earth including our bodies, respond rhythmically to the regular cycles of the sun, moon and seasons. Researchers have concluded that all living organisms are composites of rhythms with varying frequencies that may range from seconds to seasons. A number of hormones such as rennin, aldosterone and cortisol show distinct daily fluctuations. The onset and extent of disease symptoms varied in circadian rhythms [20]. It is also widely acknowledged that the effectiveness and toxicity of many drugs vary depending on the relationship between the dosing schedule and the 24 hour rhythms of biochemical, physiological and behavioral processes. The growing body of data exists demonstrating the rational behind the chronotherapeutics [21-28].

Traditionally, drug delivery has meant getting a simple chemical absorbed predictably from the gut or from the site of injection. Till now, the emphasis has been on drug delivery device that maintain constant drug level (zero order) throughout the day [29]. However, living organisms are
not “zero order” in their requirement or response to drugs. They require different amount of drug at predictably different times according to the circadian rhythms in order to maximize desired and minimize undesired drug effects [30]. Therefore, the emphasis should be placed on development of drug delivery systems that take account of variations in bodily functions during the day and night.

![Figure 1 Indication of Biological Clock](image)

**1.6.1. Chronopharmaceutics: A new branch of pharmaceutics:**

A major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of diseases or symptoms.

**1.6.2. Requirements of Ideal Chronopharmaceutical Drug Delivery System (ChrDDS):**

An Ideal ChrDDS should [116-120]:

i. be self-regulatory when taken any time of the day and should account for environmental factors such as awake-sleep, day-night, activity-rest status.

ii. be time controlled and site-specific drug delivery systems.

iii. be non-toxic within approved limits of use.

iv. have a real-time and specific triggering biomarker for a given disease state.
v. have a feedback control system (e.g. self-regulated and adaptative capability to circadian rhythm and individual patient to differentiate between awake-sleep status.

vi. be biocompatible and biodegradable especially for parenteral administration.

vii. be easy to manufacture at economic cost.

viii. be easy to administer into patient in order to enhance compliance to dosage regimen.

Till date, there is no such drug delivery in the market which fulfills all the above requirements.

1.6.3. Advantages of ChrDDS:

- Such approaches have commercial benefits for pharmaceutical companies seeking to prolong the patent life of expiring products.
- Safer, more effective and reliable therapeutic effect taking into account advances in chronobiology and chronopharmacology, system biology and nanomedicine.
- It considers person’s biological rhythms in determining the timing and the amount of medication to optimize the drug’s desired effects and minimize the undesired ones.
- Reduction of dose requirement and are likely to improve patient compliance.

The major limitation of ChrDDS is for patients who do shift works (alternate day and night) for whom chronotherapy may be too complicated.

1.6.4. Key Component for Success of ChrDDS:-

The identification of a specific time-dependent “trigger” capable of provoking drug release from oral formulation after a predetermined time interval represents a significant challenge to the pharmaceutical formulator. In the oral drug delivery field, research focuses on developing time delayed pellets, capsule and tablet dosage forms to form ChrDDS. The key component for the success of ChrDDS is the design for the treatment of diseases and the elucidation of control-relevant models for drug delivery [26]. In literature, there are several attempts of number of modeling approaches available such as modeling of hemodynamic variable regulation, cancer chemotherapy, glucose concentration control, glucose insulin interaction, rheumatoid arthritis, epilepsy, ulcer and glaucoma. These modeling approaches are very useful to design and evaluate drug delivery system that matches the biological requirement. [31]
1.6.5. Applications of Chronopharmacotherapy

- It simplifies the dosage regimen.
- It improves patient compliance.
- It improves therapeutic effect, administration, safety, and efficacy.
- It infuses new life into product.
- It boosts a drug position in marketplace.
- It controls drug release according to circadian rhythms.
- It gives a competitive edge to a product.
- It enables or accelerate market entry [32]
1.6.6. Potential disease targets:

There are several diseases which show circadian variations and are targeted for ChrDDS.

Diseases with their oscillatory rhythmicity [33-38]

1. **Allergic rhinitis** (nasal inflammation associated with hay fever): Symptoms of allergic rhinitis (e.g. nasal congestion, sneezing, runny nose) are typically more severe in the early morning hours than during the day.

2. **Asthma**: Airway resistance increases progressively at night in asthmatic patients. Exacerbation of symptoms is more common during sleep. In most patients, symptoms are 50 to 100 times more likely to occur in the last few hours before awakening than during the day.

3. **Rheumatoid arthritis**: Pain that usually peaks in morning and decreases throughout the day.

4. **Osteoarthritis**: Less pain in the morning and more at night.

5. **Peptic ulcer**: Gastric acid secretion is high during the night. Pain typically occurs after stomach emptying, following daytime meals and in the early morning, disrupting sleep.

6. **Hypertension**: Blood pressure is lowest during the sleep cycle and rises steeply during the early morning awakening period.

7. **Angina pectoris**: Chest pain and electrographic (ECG) changes are more common during the early morning. In stable angina, chest pain and ECG changes are more common during the first 4-6 hours after awakening, while in Prinzmetal’s angina, ECG changes are most common during sleep; chest pain can occur even while at rest.

8. **Myocardial infarction**: Incidence greatest in early morning.

9. **Sudden cardiac death**: Higher incidence of ventricular tachycardia are usually morning after awakening

10. **Stroke**: Incidence greatest in the early morning.

11. **Hypercholesterolemia**: Higher rate of cholesterol intake and hepatic cholesterogenesis occurs during the evening hours, even in the fasting state. Most of the bodies’ cholesterol production occurs at night.
12. **Neurological disorders**: In epilepsy, seizures often occur only at particular times of the day or night. Individual patterns differ among patients.

13. **Cancer**: In cancer, chemotherapy could be more effective and less toxic if drugs could be administered at times that take more advantages of tumor cell cycles. The studies so far suggest that there may be different chronobiological cycles for normal cells and tumor cells. If this is true, the goal would be to time the administration of cancer drugs to the chronobiological cycles of tumor cells, making them more effective against the cancer and less toxic to normal tissues.

14. **Diabetes**: In diabetic patients, providing basal insulin exogenously to inhibits hepatic glucose production. Exogenous administration of mealtime doses promotes peripheral glucose uptake (which prevents postprandial increase in blood glucose concentration) as well as reducing hepatic glucose release.

There are several drugs for which circadian variations in their pharmacokinetic and pharmacodynamic action were reported in clinical studies: includes Non steroidal anti-inflammatory drugs (NSAIDs), cardiovascular agents, antiasthmatics, psychotropic drugs, gastrointestinal agents, anticancer agents etc. (Table 1.) These lists are growing as chronobiology, chronotherapeutics and the diagnostic and treatment methods derived from them are slowly accepted by the medical community.
Table 1 Marketed formulations based on Chronopharmaceuticals [28-33]

<table>
<thead>
<tr>
<th>Products</th>
<th>Drug</th>
<th>Technology</th>
<th>Developer</th>
<th>Rationale for Chronopharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covera®HS</td>
<td>Verapamil HCL</td>
<td>OROS-CT</td>
<td>Alza Corp.</td>
<td>Hypertension/ Increased BP in early hours of the day.</td>
</tr>
<tr>
<td>Verelan®PM</td>
<td>Verapamil HCL</td>
<td>CODAS</td>
<td>Elan Corp.</td>
<td>Management of Hypertension</td>
</tr>
<tr>
<td>1. Metadate®CD</td>
<td>Methylphenidate HCL</td>
<td>DIFFUCAPS</td>
<td>Eurand Pharmaceuticals ltd.</td>
<td>Attention Deficit hyperactivity disorder (ADHD)</td>
</tr>
<tr>
<td>2. Innopran®XL</td>
<td>Propranolol HCL</td>
<td></td>
<td></td>
<td>Management of Hypertension</td>
</tr>
<tr>
<td>1. MS Contin®</td>
<td>Morphine</td>
<td>CONTIN</td>
<td>Purdue Pharma</td>
<td>Relief of Pain</td>
</tr>
<tr>
<td>2. CodeineContin</td>
<td>Codeine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Oxycontin®</td>
<td>Oxycodone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. HydromorphContin</td>
<td>Hydromorphine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Uniphyl®</td>
<td>Theophylline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardizem® LA</td>
<td>Diltiazem HCL</td>
<td>CEFORM</td>
<td>Fuisz Technologies Ltd.</td>
<td>Management of Hypertension</td>
</tr>
<tr>
<td></td>
<td>Verapamil HCL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.7. Basic gastrointestinal tract physiology

To comprehend the consideration taken in the design of the gastro retentive drug delivery system and to evaluate their performance, the relevant anatomy shown in above figure and physiology of the GI tract must be fully understood. The GI tract is essentially a tube about 9 m long that run from mouth to the anus and includes throat (pharynx), esophagus, stomach, small intestine, and large intestine. The wall of GI tract has the same general structure through most of its length from the esophagus to the anus, with some local variation for each region.

The stomach is a j-shaped dilated portion of the alimentary tract situated in the epigastric, umbilical and left hypochondriac region of the abdominal cavity. Its size varies according to the amount distention up to 1500 ml following a meal, after food has emptied; a ‘collapsed’ state is obtained with a resting volume of only 25 - 50 ml. The stomach is composed of the following parts: fundus, above the opening of the esophagus into the stomach; body, the central part; and antrum. The pylorus is an anatomical sphincter situated between the most terminal antrum and the duodenum. The fundus and body store food temporarily, secrete digestive juice and propels chyme, a milky mixture of food with gastric juice to the antrum. The antrum grinds and triturates food particles and regulates the secretion of hydrochloric acid as well as emptying of food [39]. Fasting gastric pH is specially steady and approximate 2, but there are short periods of 7 ± 6 min characterized by higher values. Food buffers and neutralizes gastric acid, thus increasing the pH
Introduction

up to 6.5. After meal ingestions completed, the pH rapidly falls back below 5 and then gradually decline to fasting state values over a period of few hour. [39]
The pyloric sphincter has a diameter of 12.8 ± 7mm in humans. The duodenal pH is 6.1; and its transit time is relatively short, less than 1 min. The small intestine has a large surface area, which is comparable to the area of basketball, 463 m². The pH of the small intestine is 6 - 7 and its transit time is 3±1 h, is relatively constant and is unaffected by food. The colon has some absorption properties of water and ions, certain drug and especially peptide molecule are also absorbed. [121-125]

1.7.1. Gastric emptying and motility of food from stomach

Gastric motility and emptying of content from the stomach is mostly contractile, which causes food grinding in to smaller particles, mixing with gastric juices, forward and backward movement of gastric content and emptying, with all of the action occurring together. Gastric emptying occurs during fasting and fed state. The pattern of motility is however differing markedly in two states. It is characterized by an interdigestive cycle both through the stomach and small intestine every 2-3 hours. [7] This motoric activity is called as interdigestive myoelectric cycle or migrating myoeletric cycle (MMC) or interdigestive myoelectric motor complex (IMMC). Its aim is to clear the stomach and the small intestine of indigested debris, swelled saliva and sloughed epithelial cell. [39]

It is composed of four phases,

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contraction.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contraction. As the phase progress the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contraction for short period. Due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 minutes and occurs between phase III and I of two consecutive cycles [40].
1.7.2. Factors affecting gastric retention

There are several factors that can affect gastric emptying and gastric retention time (GRT) of oral dosage form. The factor that affects gastric retention time include density, size and shape of dosage form, concomitant intake of food and drug, other factors such as gender, posture, age, body mass index and disease state also affect gastric retention [41]. Generally female have slower gastric emptying rate than males. Stress increase gastric emptying rate while depression slow it down. A numbers of factors affect gastric retention of orally administered dosage form which is shown in table 2 [42].

Table 2 Factors Affecting Gastric Retention Time (GRT)

<table>
<thead>
<tr>
<th>Factors Affecting GRT</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of food</td>
<td>Larger the starting volume greater the initial rate of gastric emptying.</td>
</tr>
<tr>
<td>Food containing Fatty acid</td>
<td>Reduction in the rate of emptying in direct proportion to carbon chain length.</td>
</tr>
<tr>
<td>Food containing Triglycerides</td>
<td>Reduction in rate of emptying.</td>
</tr>
<tr>
<td>Food containing Carbohydrate</td>
<td>Reduction in rate of emptying as a result of osmotic pressure.</td>
</tr>
<tr>
<td>Food containing Amino Acid</td>
<td>Reduction in rate of emptying as a result of osmotic pressure.</td>
</tr>
<tr>
<td>Physical state of Contents</td>
<td>Solution or Suspension of small particle empty more rapidly.</td>
</tr>
<tr>
<td>Acids</td>
<td>Reduction in gastric emptying rate depends upon concentration and Molecular weight of the acid.</td>
</tr>
<tr>
<td>Alkali (NaHCO₃)</td>
<td>Increase rate of emptying at low concentration (1%) and decrease rate at higher concentration (5%).</td>
</tr>
<tr>
<td>Anticholinergic</td>
<td>Reduction in rate of emptying.</td>
</tr>
<tr>
<td>Narcotic analgesic</td>
<td>Reduction in rate of emptying.</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Increase in rate of emptying.</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Reduction in rate of emptying.</td>
</tr>
<tr>
<td>Salt and electrolytes</td>
<td>Rate of emptying way increase at lower concentration and then decrease at higher concentration.</td>
</tr>
</tbody>
</table>
Viscosity | Rate of emptying is greater for less viscous solution.
---|---
Body position | Rate of emptying is reduced in patient lying on left side.
Bile salt | Rate of emptying is reduced.
Gastric surgery | Gastric emptying difficulties can be serious problem after surgery.

### 1.7.3. Gastroretentive drug delivery system (GRDDS)
Recent scientific and patent literature shows increased interest in academics and industrial research groups regarding the novel dosage forms that can be retained in the stomach for a prolonged and predictable period of time. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT), using gastroretentive drug delivery system (GRDDS) that will provide us with new and important therapeutic options [41].

Gastroretentive system can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It has applications for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients [40].

### 1.7.4. Pharmaceutical aspects of gastroretentive drug delivery system (GRDDS)
In designing GRDDS, the following characteristics should be sought: convenient intake, retention in the stomach according to clinical demand; ability to load substantial amount of drugs with different physicochemical properties and release them in controlled manner; complete degradation, preferable in the stomach [39].

Gastric retention will provide advantages such as the delivery of drug with narrow absorption window in the small intestinal region. Also longer residence time in the stomach could be advantages for local action in the upper part of small intestine; e. g. in the treatment of peptic ulcer disease, further more improved bioavailability is expected for drug that absorbed readily upon release in the GI tract. To achieve gastric retention, the dosage form must satisfy certain requirements one of the key issue is that the dosage form must be able to withstand the force
caused by peristaltic waves in the stomach and the constant contraction, grinding and churning mechanism.

1.7.5. Approaches to gastric retention
Various approaches have been followed to encourage gastric retention of an oral dosage form in the stomach, including

![Schematic localization of an intra-gastric floating system and high density system in the stomach](image)

Figure 4 Schematic localization of an intra-gastric floating system and high density system in the stomach

i. Mucoadhesive/bioadhesive drug delivery system.
ii. Swelling and expanding drug delivery system.
iii. High density system.
iv. Delayed gastric emptying system.
v. Floating drug delivery system in detail.

i) Mucoadhesive/bioadhesive drug delivery system

Bioadhesion is the phenomenon in which two materials, at least of which is biological are held together by means of interfacial force. The attachment could be between a biological substrate and artificial material, such as adhesion between a polymer and biological membrane. In the case of polymer attached to the mucin layer of a mucosal tissue, the term mucoadhesion is used. [43]
Bioadhesive drug delivery systems (BDDS) are used to localize a delivery device within the lumen to enhance drug absorption in a site specific manner [44]. Suitable polymers that can be used to form mucoadhesive microsphere include soluble and insoluble, non-biodegradable and biodegradable polymers. This can be hydrogels, thermoplastics, homopolymers, copolymers and natural synthetic polymers, [42] polycarbophil, carbopol, lectin, chitosan, CMC [45].

ii) **Swelling and expanding drug delivery system**

To achieve gastroretention the most promising approach is that of creating a swelling and expanding system. Any system will need to expand to a size large enough to be retained in the (fasted) stomach, but to do so in a safe and reliable manner. It must not swell or expand in the esophagus or in the intestine; if it is emptied prematurely from the stomach (e.g. Problem could arise from the formation of an insoluble mass known to bezoars). The gastroretentive system will also need to display controlled release properties so that the drug is released at an appropriate rate for optimal absorption window. The systems should have an ability to remain in the stomach and withstand the mechanical force therein. Last but not least, it will need to decrease in size after it has performed its function and transit through the intestine in the normal way [46].

iii) **High density system**

The use of dosage forms of high density that might remain in the stomach longer when positioned in the lower part (shown in Figure 4) of the antrum has been proposed as a means to increase the GI transit duration. The effectiveness of this approach has not been confirmed [47].

iv) **Delayed gastric emptying system**

The use of passage-delaying excipients has been proposed as an attempt to develop a form that exerts some influence on its own transit. Preliminary in vivo result depicts a major problem related to the highly variable inter-subject reactions. Another analogue approaches consist of using passage delaying drug, for example propantheline, which is generally considered undesirable because of potential side effects [47].
1.8. Floating Drug Delivery System [126-135]

The concept of floating drug delivery systems (FDDS) was first described in the literature in early 1968, when Davis disclosed a method for overcoming the difficulty experienced by some persons of gagging or choking while swallowing medical pills. The author suggested that such difficulty could be overcome by providing pill having a density less than 1.004 g/cm$^3$, so that pill will float on water.

1.8.1. Classification of floating drug delivery system (FDDS)

1. Effervescent Floating Dosage Forms

These buoyant drug delivery systems utilize matrices prepared with swellable polymers such as methyl cellulose, polysaccharides, chitosan and various effervescent compounds, e.g., sodium bicarbonate, tartaric acid, or citric acid or matrices containing chambers of liquids that gasify at body temperature. The matrices are fabricated so that upon arrival in the stomach, CO$_2$ is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloids. This produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on the chyme. [48]

2. Non-Effervescent Floating Dosage Forms

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type of hydrocolloids, polysaccharides, and matrix-forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density <1gm/cm$^3$. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass [41].

1.8.2. Floating-Pulsatile Drug Delivery System

Recent studies in the area of oral controlled drug delivery include novel approaches, which prolong the GRT and Chronotherapeutict delivery system which release the drug in a pulsatile
fashion, is recently gaining much attention worldwide. Pulsatile drug delivery system are characterized by two release phases, a first phase with no or little drug being released, followed by a second phase, during which the drug is released completely within a short period of time after the lag time.

Various diseases like asthma, hypertension, and arthritis show circadian variation, that demand time scheduled drug release for effective drug action for example inflammations associated with morning body stiffness, asthma, and heart attack in early hours of the day. Result of several epidemiological studies demonstrates the elevated risk of several pathologies during a 24 h cycle. Specifically, symptoms of rheumatoid arthritis and osteoarthritis, dyspnoea and epilepsy appear to have a peak during the night or early in the morning. Ischemic disease such as angina pectoris and myocardial infarction, and manifested more frequently during these times. Blood pressure which arises notably just before waking up is usually responsible for these attacks. Aceclofenac was chosen as a model drug, which is effective for preventing the time related occurrence of rheumatoid arthritis and osteoarthritis. Aceclofenac was widely accepted as a NSAID agent. So Aceclofenac is a typical example of drug, which is used in the therapy of symptoms or disease as described. However for such cases, conventional drug delivery system are inappropriate for the delivery of Aceclofenac, as they cannot be administered just before the symptoms are worsened, because during this time patient are asleep.

To follow this principle one must have to design the dosage forms so that it can be given at the convenient time for example bed time for the above mentioned diseases with the drug release in the morning. Using current release technology, it is possible for many drugs oral delivery for a pulsed or pulsatile release, which is defined as the rapid and transient release of a certain amount of drug within a short time-period immediately after a predetermined off-release period. Chronotherapeutical devices based on multiphase drug release were achieved by using a three layer tablet while similar devices were also developed. Time controlled coating system was also developed including single and multiple unit dosage forms [49].

**1.8.3. Application of floating drug delivery system**

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 Release 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 <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 [40].

- **Site-Specific Drug Delivery**
  Floating drug delivery system is particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, e.g., riboflavin and furosemide [40].

- **Absorption Enhancement**
  Drugs that have poor bioavailability because of sites 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. FDDS also serves as an excellent drug delivery system for the eradication of Helicobacter pylori, which causes chronic gastritis and peptic ulcers. The treatment requires high drug concentrations to be maintained at the site of infection that is within the gastric mucosa. By virtue of its floating ability these dosage forms can be retained in the gastric region for a prolonged period so that the drug can be targeted [40].

1.8.4. **Limitations of floating drug delivery system**

Floating drug delivery system is associated with certain limitations which are,

1. Drugs that have multiple absorption sites in the gastrointestinal tract, and those that are not stable at gastric pH are not suitable candidates to be formulated as floating dosage forms.

2. One drawback of hydro dynamically balanced systems is that, this system being a matrix formulation consists of a blend of drug and low-density polymers. The release kinetics of drug cannot be changed without changing the floating properties of the dosage form and vice versa. [40]
Marketed products of FDDS: [10]
The last three decades of intensive research work have resulted in the development of five commercial FDDS, presented in table 3.

Table 3 Marketed products of floating drug delivery system.

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madopar</td>
<td>Antiparkinsonism</td>
</tr>
<tr>
<td>Valrelease</td>
<td>Sedative, hypnotic</td>
</tr>
<tr>
<td>Liquid Gaviscon</td>
<td>Suppress gastroesophageal reflux &amp; heart burn</td>
</tr>
<tr>
<td>Topalkan</td>
<td>Antacid, Antiseptic</td>
</tr>
<tr>
<td>Almagate Flotcoat</td>
<td>Antacid</td>
</tr>
</tbody>
</table>

1.9. Pellets, Tablets, Pelletization and Compression:
The word pellet has been used to describe a variety of systematically produced, geometrically defined agglomerates, obtained from diverse starting materials utilizing different processing conditions.

Pelletization is an agglomeration process that converts fine powders or granules into small, free flowing, spherical or semi spherical units, referred to as pellets. [34]

Various industries such as chemical, confectionary, agricultural etc. have widely utilizing pelletization technique since early 20th century to manufacture particles of defined sizes and shapes. In the pharmaceutical industries, spherical oral dosage form such as pills have been used for a long time, but it was only in the early 1950s, the pharmaceutical industry developed keen interest in pelletization technology. A major breakthrough occurred in 1949 when a pharmaceutical firm Smith Kline and French (SKF) realized the potential application of pellets in sustained release preparation and received a series of patents [51-54].

As a result, pellet production technology has greatly evolved from simple pan coating to a recent "Marumerizer" commonly called as "Spheronizer" developed in Japan and capable of producing large quantities of spherical pellets in relatively short span of time.
As the drug delivery systems became more sophisticated, the role of pellets in dosage form design and development increased substantially.

1.9.1. Advantages of Pellets: [55]

i] Pellets offer better statistical assurance of complete drug release as the risk of dose dumping is minimized.

ii] High local concentration of drug, which may inherently be irritating, can be avoided.

iii] As pellets uniformly distribute thought the gastrointestinal tract, they invariably maximize drug absorption, reduce peak plasma fluctuations and minimize potential side effects without appreciably lowering bioavailability.

iv] Control release pellets enable a smoother absorption sorption profile.

v] Pellets also reduce variation in gastric emptying rates and overall transit times, so that intra and inter subject variability of plasma level is minimized.

vi] Release rate from pellets can be manipulated as desired by blending pellets having different release rates in suitable proportion.

vii] Combined delivery of two or more bioactive agent, which may or may not be chemically compatible at the same site or at different site within gastrointestinal tract is possible.

viii] Pelletized product can be made to meet the aesthetic appeal by imparting shades of color during manufacturing process.

ix] Pellets ensure improved flow properties and flexibility in formulation development and manufacturing.

1.9.2. Pelletization Technology [56]

The pelletization technology is useful in the following cases:

1. Controlled Release Products:

- The pellet form provides a smoother absorption profile from the gastrointestinal tract as the beads pass gradually through the stomach into the small intestine at a steady rate.
- In contrast the whole tablet is released at once into the small intestine as the stomach empties itself.
• Different types of pellets can be coated with different drugs to enable the controlled release rate. All these can be combined in a single capsule to obtain the desired results.

2. Immediate Release Products:
• Administering the drugs in the pellet form leads to consumption of the drug which has an increased surface area as compared to traditional compressed tablets and capsules.
• This would considerably reduce the time required for disintegration.

3. Chemically Incompatible Products:
• At times such ingredients are required to be delivered in a single dose.
• In the conventional tablet dosage separate tablets would have to be administered but the pellets can be administered in a single capsule.

4. Varying dosage without reformulation:
• Pellets have excellent flow properties. Due to this they can be conveniently used for filling capsules & the manufacturer can vary the dosage by varying the capsule size without reformulating the product.

1.9.3. Pelletization Process [50]
The most widely used pelletization processes in pharmaceutical industries are extrusion/spheronization, solution or suspension layering and powder layering. Other process with limited application in the development of pharmaceutical pellet includes globulation, balling and compression. Extrusion/Spheronization is rapid and advanced process and is the method of choice for the drugs having higher doses and where economics of production is aimed. The fig. 5 shows the classification of pelletization processes.
1.9.4. Pelletization by Extrusion Spheronization [57, 58]
Extrusion spheronization is basically a wet granulation process called as "Marumerization" (round making). The process consists of following stages: dry blending of the active substance(s) with excipients, wet granulation of mass, extrusion of moist mass, rolling of the extrudate in the spheronizer and drying of pellets. Dry blending and wet granulation steps are similar to those used to prepare tablet granulations.

Figure 5 Classification of various pelletization processes

1.9.5. Extrusion [136-139]
Extrusion is a process, which produces cylindrical extrudate of desired length and diameter when wet mass is forced through a perforated mesh. The instrument, which produces extrudate, is called as extruder. Four types of extruders are available, these are:

I. Screw extruders
II. Sieve and basket extruders
III. Ram extruders
IV. Roller extruders

1.9.6. Spheronization [59]
Spheronization is a process, which convert cylindrical extrudate into spherical pellets when subjected to spiral rope like motion in the spheronizer.
The machine consists of a round disc with vertical shaft, spinning at high speed at the bottom of a cylindrical chamber. The cylindrical chamber is called "bowl" and the spinning disc is called "Friction plate". The friction plate has grooved pattern to increase the friction with product. When the extrudate are changed into spheronizer, they fall on to the spinning plate and are thrown towards the periphery due to the centrifugal force. Mechanical energy introduced by the spinning friction plate is transmitted into kinetic energy in the form of a mechanically fluidized bed, resembling more or less like a random mixture of air borne particles moving at high velocity. Due to contact with the plate, the extrudates are cut into short cylindrical segments, which are gradually rounded by collision with the bowl wall and plate. During the first contact of the cylindrical extrudes with friction plate, the extrudate are cut into segment with a length ranging from 1 to 1.2 times the diameter. These segments then collide with the bowl wall and they are thrown back to the inside of the friction plate. The ongoing action of particles colliding with the wall being thrown back to the inside of the plate creates a "rope like movement" of product along the blow wall. This continuous collision of the particles on the wall and with the friction plate will gradually turn the cylindrical segment into spheres, provided that the granules are plastic enough to allow the deformation without being destroyed. After certain retention time, the particles obtain the desired spherical shape, the discharge valve of the chamber is then opened and the granules are discharged by the centrifugal force. It might happen that in the first phase of the process, fines are generated in the chamber. These fines will either adhere to the surface of the spheres or they can get under the friction plate, through the gap between plate and wall. The fines under the friction plate will be discharged from the machine by means of a propeller.

1.9.7. Dry coated triple layer floating pulsatile release tablet by direct compression.
Dry coated floating pulsatile release tablet was prepared by using compression coating method. Direct compression consists of compressing tablets directly from powdered material without modifying the physical nature of the material itself. Direct compression as a method of tablet manufacture was reserved for a small group of crystalline chemicals having all the physical characteristics required for the formation of a good tablet [60].
1.9.8. Excipients for Preparation of Pellets & Tablets [61, 62]

Excipients are added to pharmaceutical dosage forms mainly to produce satisfactory delivery of drug to the intended site, to impart favorable characteristics to the dosage form and to facilitate the manufacturing of the products.

Excipients used for pellets are typically the same as used for tablet or capsule formulation. Excipients selection for a particular product should be made judiciously as it affects the characteristics of final product like hardness, friability, size and shape and dissolution profile. Examples of different excipients are shown in Table 4.

Table 4 Excipients for preparation of pellets & Tablets

<table>
<thead>
<tr>
<th>Excipients</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fillers</td>
<td>Dibasic calcium phosphate, Lactose, Mannitol, Microcrystalline cellulose, Starch, Sucrose</td>
</tr>
<tr>
<td>Binders</td>
<td>Gelatin, Hydroxy propyl cellulose, Hydroxy propyl methyl cellulose, Polyvinyl pyrolidone</td>
</tr>
<tr>
<td>Lubricants</td>
<td>Calcium stearate, Glycerin, Magnesium Stearate, Polyethylene glycol, Propylene glycol, Hydrogenated vegetable oil</td>
</tr>
<tr>
<td>Separating agents</td>
<td>Kaolin, Talc, Silicon dioxide</td>
</tr>
<tr>
<td>Disintegrants</td>
<td>Croscarmellose sodium, crosspovidone, Sodium starch glycolate</td>
</tr>
<tr>
<td>pH modifiers</td>
<td>Citrates, Phosphates</td>
</tr>
<tr>
<td>Surfactants</td>
<td>Polycarbonates, Sodium lauryl sulphate</td>
</tr>
<tr>
<td>Spheronization enhancers</td>
<td>Microcrystalline cellulose, Sodium carboxy methyl cellulose</td>
</tr>
<tr>
<td>Glidants</td>
<td>Colloidal silicon dioxide, Magnesium stearate</td>
</tr>
</tbody>
</table>
1.9.9. Evaluation of Pellets & Tablets [63-66]

Pellets & Tablets were evaluated for certain quality measures, which reflect the suitability and endurance of material during various operations like filling transportation and handling. These physical characteristics can be correlated with formulation properties and operating conditions and can be used to optimize these variables to insure a product with reproducible properties. The most common physical characteristics evaluated for pellet are:

i] Size and size distribution

Pellet are invariably coated, may it be for aesthetics, enteric release, taste masking, stability or controlled release. In order to achieve any of these desired end product performances, it is necessary to determine the amount of coating material required to produce the desired film thickness and or coverage, since particle size directly affects surface area and consequently the amount of necessary coating material. It is advantageous to use the largest possible particle size for the substrate that may provide desired end product performance. However the size distribution should be as narrow as possible for several reasons.

a. A narrow size distribution will ensure minimum variation in coating thickness in the batch.

b. Reduced segregation during filling or mixing.

Pellet size distribution is commonly determined by sieving and microscopy methods.

ii)] Density

Density of pellets can be affected by changes in formulation and or process variable. Bulk density is important criteria as it can significantly affect fill volumes and can affect batch size determination during coating operation. It is also important if mixing of different type of pellets prior to filling is involved, as differences in bulk density can led to segregation.

The most commonly used method for bulk density determination is the tapping method. In this measured weight of pellets is poured into a graduated cylinder and the initial volume is noted. Then the cylinder is tapped and the tapped volume is noted. The former observation gives poured packing density while the later gives tapped density. Variations exits in the literature with regard
to the number of taps used. However a general convention is to use number of taps, which assure reproducibility.

iii] **Flow Property**
Flow property reflects suitability of material during filling operation. Also it reflects changes in particle size, shape, density, electrostatic charges and adsorbed moisture, which may arise from processing or formulation changes.

The more commonly used method to assess flow property is angle of repose. It is best satiated for particles having size above 150 µm. The value of angle of repose below 30° reflects excellent flow ability and above 40° indicates poor flow ability.

iv] **Friability and Hardness**
It is necessary to attain acceptable friability of pellets that can withstand handling, shipping, storage and operations as coating and filling. Friability is strongly affected by type and amount of binder used. It is also affected by processing method.

Friability is generally determined by use of Roche Friabilator. It involves placing measured weight of pellets in the friabilator and rotating it for a predetermined number of revolutions and then measuring the weight of intact pellets. The difference in weight is expressed as percentage. The generally accepted upper limit for pellets is 1% w/w.

v] **Porosity**
Porosity of pellets can affect the capillary action of the dissolved drug and consequently influence the rate of release of drug from pellets. It also affects film deposition and formation during coating. The pores can be analyzed qualitatively by scanning electron microscopy and quantitatively by mercury intrusion porosimetry.

vi] **Surface area**
Surface area of pellets affect drug release rate and flow rate of pellets. Surface area of pellets can be controlled by particle size, shape, porosity and surface roughness. Surface area of pellets drastically affects the film deposition and formation during coating. Surface area of pellets can be determined by particle size distribution, gas adsorption and air permeability methods.
Shape of pellets can be analyzed using an image analyzer. The other methods used for determining the shape of pellets are ring gap analyzer, scanning electron microscopy (SEM).

1.9.10. COATING: [70]
Coating is one of the oldest pharmaceutical processes still in existence. This skilled art, which was originally carried out for decorative purpose, has evolved into much more sophisticated and controlled process. The design of new equipment, development of new coating materials, advances in technology have all contributed to improved products.

A market survey reveals that a significant proportion of solid dosage forms available are coated. As coating is an additional step in manufacturing process, it increases the cost of product; therefore, decision to coat the dosage form is usually based on one of the following objectives:

- To improve drug stability by protecting from gastric and atmospheric environment (air, light, moisture)
- To reduce risk of interaction between incompatible ingredients
- To improve patient compliance by increasing ease of ingestion, masking unpleasant taste and odor
- To improve product appearance
- To modify drug release, as in enteric coated, controlled or sustained release dosage form

**Enteric coating** [71, 72]
Enteric coating is those that remain intact in stomach but will dissolve and release the contents of dosage form, once it reaches the small intestine. The action of enteric coating results from a difference in composition of the respective gastric and intestinal environment in regard to pH and enzymatic properties. Reasons for enteric coating on drug products

- a. Preventing the destruction of drug by gastric pH and enzymatic degradation.
- b. Preventing nausea and vomiting caused by drug irritation of the gastric mucosa.
- c. Delivering the drug i.e. primarily absorbed in the intestine to that site in the highest possible concentration.
- d. Providing delayed release of drug
The most extensively used polymers for enteric coating is cellulose acetate phthalate, hydroxypropylmethyl cellulose acetate phthalate, poly vinyl acetate phthalate etc. [71]

Now days, specific EUDRAGIT acrylic polymers have been developed for peroral dosage form with stepwise release of active ingredients in the digestive tract. The eudragit coating is soluble as a function of environmental pH value. Eudragit polymers can be applied as coatings to all conventional, solid oral dosage forms such as tablets, capsules, small particles. These polymers can also be used to manufacture pellets, granules, and sustained-release tablets.

For enteric coating, Eudragit polymer dissolves at rising pH values

- Release of active ingredients in the duodenum with EUDRAGIT L 100-55 or the aqueous dispersion EUDRAGIT L 30 D-55 at pH values over 5.5.
- Release of active ingredients in the jejunum to ileum with EUDRAGIT L 100 at pH values over 6.0 or with mixtures of EUDRAGIT L 100 and EUDRAGIT S 100 in a pH range from 6.0 to 6.5.
- Release of active ingredients near the colon with EUDRAGIT S 100 in a pH range from 6.5 to 7.5.

These EUDRAGITS are anionic polymers based on methacrylic acid esters. The films are soluble below pH 5 and thus resistant to gastric fluid. By salt formation in the neutral to weakly alkaline medium of intestinal fluid, the films dissolve step-wise at pH values above 5.5.

**EUDRAGIT L 100/S 100:** These Eudragit show excellent sealing effect even at very thin layers. This enables the following technical effects to be obtained:

- Protection against atmospheric humidity
- Isolating mutually incompatible particles in combination products.
- Masking of cores with an unpleasant odour or taste
- Granulation of active ingredients in powder form.

EUDARGIT Polymethacrylate can be processed in all conventional types of coating equipment, by all coating operations commonly performed in the pharmaceutical industry. Coating pans with spraying devices and high drying air capacity are particularly suitable for tablets. Fluid-bed
coaters are preferred for the small particles, which show a more pronounced tendency to agglomeration. [72]