1. INTRODUCTION

Most conventional oral dosage forms, such as tablets and capsules are formulated to release the active drug immediately after oral administration to obtain rapid and complete systemic drug absorption.\(^1\) Such immediate-release products result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity.\(^2\)

An alternative to administering another dose is to use a dosage form that will provide controlled/sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms. In recent years, various modified-release drug products have been developed to control the release rate of the drug and/or the time for drug release.

Advanced drug delivery systems have more advantages than the conventional delivery system. Ideally they may improve drug potency, controlled drug release over to a sustained periodic of time, provide greater safety and reduced toxic effects. Drugs can also be targeted to a specific tissue in the human system.\(^3\)
CONTROLLED DRUG DELIVERY SYSTEMS

Controlled delivery can be defined as

- Sustained action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with minimization of undesirable side effects\(^4\)
- Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue\(^5\)
- Targeted drug action by using carriers to deliver drug to a particular target cell
- Provide a physiologically / therapeutically based drug release system

Advantages of Controlled Drug Delivery Systems\(^6,7\)

- Overcome the patient compliance problems
- Therapeutic advantage
- Reduction in the adverse side effects
- Reduced 'see-saw' fluctuation
- Reduced total dose
- Improved efficiency in treatment
- Reduction in health care cost

Disadvantages\(^8,9\)

- Dose dumping
- Less flexibility in accurate dose adjustment
- Poor In Vitro – In Vivo correlation
- Patient variation
The development of oral controlled drug delivery systems will lead:

- Improved patient convenience
- Reduced dose
- Increased safety margin due to decreased adverse effects and toxicity
- Improved bioavailability of the drugs.
- Reduction in health care costs in certain cases

Ideal Characteristics of Controlled Drug Delivery

a) Desirable half-life
The half-life of a drug is an index of its residence time in the body. Drugs with half-life of 2 to 8 hours are suitable for controlled and sustained delivery. However in some cases some other pharmacological parameters also considered irrespective of the half-life.10

b) High therapeutic index
Drugs with low therapeutic index are unsuitable for incorporation in controlled release formulations. If the system fails in the body, dose dumping may occur, leading to unwanted side effects and sometimes it may be fatal also. eg. Digitoxin.8

c) Small dose
If the dose of a drug in the conventional dosage form is high, its suitability as a candidate for controlled release is seriously undetermined. This is chiefly because the size of a unit dose controlled release formulation would become too big, to administer without difficulty.11
d) **Desirable absorption and solubility characteristics**

Absorption of poorly water soluble drug is often dissolution rate limited. Incorporating such compounds into controlled release formulations is therefore unrealistic and may reduce overall absorption efficiency.\(^\text{12}\)

e) **Desirable absorption window**

Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the ‘absorption window’. Drugs exhibiting an absorption window like fluorouracil, thiazide diuretics, if formulated as controlled release dosage form are unsuitable

f) **First pass metabolism**

Delivery of the drug to the body in desired concentrations is seriously hampered in case of drugs undergoing extensive hepatic first pass metabolism, when administered in controlled release forms.\(^\text{13}\)

**PHARMACOKINETIC MODELS**

The pharmacokinetic models for controlled release includes zero order, first order, Higuchi, Korsmeyer- Peppas model, Hixson Crowell, Baker-Lonsdale, Weibull model.\(^\text{14}\)

Currently available controlled drug delivery systems are floating tablets, osmotic tablets, matrix tablets, colonic release, plastic matrices, ion exchange resin tablets, film coated tablets, enteric coated and delayed release tablets, swellable tablets, mucoadhesive tablets, multiple unit tablets, repeat action tablets, floating capsules, microgranules, spheroids, beads, pellets, microcapsules, microspheres and nanoparticles.
NANOPARTICLES

Nano as the name itself implies that these systems are in nano size. Nanotechnology is a broad field which involves variety of applications including drug delivery, medical diagnostics etc. These systems have some peculiar properties such as increased surface area, specific targeting, optical properties and less toxicity when compared to other systems. In 1974, Norio Taniguchi used the term nanotechnology at first time. Nano systems provide an efficient way of drug delivery particularly for chronic therapy management.

In nano systems, nanoparticles are of one type which delivers the drug in systematic manner. Nanoparticles are small colloidal particles which are made of biodegradable and/or non-biodegradable polymers in which the drug is entrapped, dissolved, dispersed or encapsulated to a polymeric matrix. Usually the particle size ranges from 1 to 1000nm.

Nanoparticles are preferred over liposomes because of its stability, protection capability of drug from degradation and high encapsulation efficiency.

Natural polymers like albumin, gelatin, lecithin, alginate, chitosan, dextran, agarose and synthetic polymers like PLGA, PLA, PGA, PMMA are commonly used in the preparation of nanoparticles.
Advantages 18, 19

- Improved bioavailability
- Targeting to specific site
- Immediate / controlled / sustained release can be achieved
- Longer stability period
- High drug loading
- Different types of drugs can be incorporated
- Can be administered through different routes

Disadvantages 19, 20

- Requires high skilled persons
- Higher manufacturing costs. Usually suitable for high cost drug
- Complicated procedure for manufacturing
- Particle-particle aggregations
- Traces of solvents and stabilizers may produce toxicity

PREPARATION OF NANOPARTICLES

Nanoparticles can be prepared by different methods. But in any case, certain factors should be considered.

- Particle size required
- Properties of drug such as solubility, $pK_a$ etc.
- Properties of polymer such biodegradability, biocompatibility and toxicity
- Properties of other additives viz. stabilizer which determines the stability of the product
- Manufacturing method to be used
The commonly employed methods for the preparation of nanoparticles are

- Emulsion-solvent evaporation method
- Emulsion- Diffusion method
- Precipitation method
- Salting out method
- Spray drying
- Polymerization method

**Emulsion - Solvent Evaporation Method**

This is one of the common and frequently used methods for the preparation of nanoparticles. This method involves dispersion of drug in preformed polymer solution followed by emulsification into an aqueous solution. Then the solvent used for dissolving polymer is evaporated which results in precipitation of nanoparticles. The precipitated nanoparticles are collected by ultracentrifugation. Then it is washed to remove the unnecessary residues and then lyophilized. Slight modification of this method can be done by adding aqueous drug solution to polymer solution under continuous stirring to form single emulsion followed by adding it to second aqueous solution to form double emulsion. Then it is ultra-centrifuged, washed and lyophilized as per the usual procedure. This method is referred as double emulsion-solvent evaporation.

**Emulsion - Diffusion Method**

In this method, the polymer is dissolved in partially water miscible solvent, saturated with water and emulsified in aqueous solution containing emulsifier. This step may lead to spontaneous diffusion of solvent, which in turn produces nanoparticles. The solvent is then
removed by filtration and/or evaporation. Usually this technique produces nanoparticles of high encapsulation efficiencies.

**Precipitation Method**

In precipitation method, polymer, active medicament and/or lyophobic surfactant are dissolved in water miscible solvent. This solution is added slowly to an aqueous solution containing stabilizer under continuous stirring. Nanoparticles are formed due to rapid solvent diffusion. Hence this method can also be called as solvent diffusion. Then the solvent is removed from the suspension under reduced pressure. The rate of addition of one phase to another may affect particle size as well as entrapment efficiency.

**Salting Out Method**

Most of the nanoparticle preparation methods involve organic solvents, surfactants which may be hazardous to the environment. In this method, an aqueous solution containing electrolytes and viscosity building agents is added to the water miscible solvent containing polymer under vigorous stirring. The electrolytes in the aqueous solution prevent the miscibility of two phases. Formation of nanoparticles was caused by salting out mechanism.

**Spray Drying**

The concept involved in this method is formation of dry particles by instantaneous evaporation of solution droplet sprayed from spray drier specified for this purpose. The solution is atomized to produce tiny droplets and spray dried using spray dryer. All steps including drying occur within seconds. Hence, this technique may be suitable for thermolabile drugs. The solvent properties and nature may have an effect on particle morphology. No purification is required in this method.
Polymerization Method

Nanoparticles can also be formulated by polymerization method. The monomers can be polymerized to polymers. In this method, the drug is dissolved in polymerization medium which contains monomer. The incorporation of drug can be done at before addition of monomer or at final stage of polymerization reaction. Then the nanoparticles are purified by ultracentrifugation, washed and lyophilized.\textsuperscript{27}

CHARACTERIZATION OF NANOPARTICLES

The following parameters are to be considered in characterizing nanoparticles.

- Particle size
- Particle Morphology
- Zeta potential
- Entrapment efficiency
- Drug release

Particle Size

The size of the nanoparticle affects both \textit{in vitro} and \textit{in vivo} characters. So it is mandatory to achieve the required nano size. The size can be measured by photon correlation spectroscopy, laser diffraction, coulter counter. The shape of a particle can be visualized by atomic force microscopy.\textsuperscript{28} Change in particle size may lead to stability problems.

Particle Morphology

Morphology of the particle can be studied by scanning electron microscopy, transmission electron microscopy or by atomic force microscopy (AFM). By AFM, high resolution
images can be obtained. Crystallinity and polymorphic studies can be performed by using x-ray diffraction.\textsuperscript{29}

**Zeta Potential**

This parameter directly relates to the stability of the product. Increased particle size, particle-particle aggregation can be avoided by high zeta potential nanoparticles. Zeta potential can be measured by zeta sizer.\textsuperscript{30} Drug and stabilizers used in the formulation may have an abundant effect in the zeta potential values. When zeta potential value increases, ultimately the particle surface charges increases, which results in stable preparation. To maintain the increased zeta potentials, stabilizers are used.

**Entrapment Efficiency**

This parameter gives information about the entrapment of drug in the polymer. Entrapment efficiency gives valuable information about the type and amount of carrier to be used for particular drug.\textsuperscript{31} It depends on drug solubility, polymer composition, molecular weight and drug polymer interaction.

**Drug Release**

Nanoparticles concept also emerged to solve the poor solubility issues of a drug. The solubility can be increased by reduced particle size. So it is important to achieve the dissolution of required amount of drug to the target site. If a nanoparticle is designed for controlled effect, then the release should be achieved in controlled manner at the systemic site. This can be achieved by coating a polymer or by some other mechanisms. The drug release can be determined by dissolution, diffusion or ultracentrifugation.\textsuperscript{32}
PURIFICATION AND STERILIZATION OF NANOPARTICLES

Nanoparticles are prepared by using organic solvents, stabilizers which may produce severe toxic effects. So in manufacturing of nano systems it is one compulsory step to purify and sterilize the product. The purification step eliminates the organic solvents, stabilizers and other toxic impurities from the nanoparticles. The purification can be made by using common methods like gel filtration, ultracentrifugation and dialysis. The sterilization of nanoparticles can be achieved by membrane filtration or by autoclaving in aseptic area.

APPLICATIONS OF NANOPARTICLES

The following categories of drugs are prepared as nanoparticles.

Table 1.1 Applications of Nanoparticles

<table>
<thead>
<tr>
<th>Category/Use</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-ulcer\textsuperscript{35,36,37}</td>
<td>Lansoprazole, Famotidine, Cimetidine</td>
</tr>
<tr>
<td>Anti-inflammatory\textsuperscript{38,39,40,41,42}</td>
<td>Aceclofenac, Diclofenac, Ketoprofen, Dexamethasone, Piroxicam</td>
</tr>
<tr>
<td>Anti-alzheimer\textsuperscript{43,44}</td>
<td>Tacrine, Rivastigmine</td>
</tr>
<tr>
<td>Anti-tubercular\textsuperscript{45}</td>
<td>Isoniazid, Pyrazinamide, Rifampicin, Ethanmbutol</td>
</tr>
<tr>
<td>Anti-diabetic\textsuperscript{46,47}</td>
<td>Glibenclamide, Gliclazide</td>
</tr>
<tr>
<td>Anti-diuretic\textsuperscript{48}</td>
<td>Frusemide</td>
</tr>
<tr>
<td>Anticancer\textsuperscript{49,50,51,52}</td>
<td>Flutamide, Curcumin, Paclitaxel, Cytarabine</td>
</tr>
</tbody>
</table>
GASTROINTESTINAL TRACT (GIT)

The gastrointestinal tract (GIT) consists of a hollow muscular tube starting from the oral cavity, where food enters the mouth, and ends with anus where food is discharged, in between consists of the pharynx, oesophagus, stomach and intestines to the rectum.

![Diagram of the Gastrointestinal Tract](image)

**Fig. 1.1 Gastrointestinal tract**

The human gastrointestinal tract (GI tract) is divided into the upper and lower gastrointestinal tracts. It’s illustrated in the figure given below.
Upper gastrointestinal tract

*Esophagus, Stomach, and duodenum*

The esophagus is a tube composed of muscles and approximately 250mm in length and 20mm in diameter. It extends from the pharynx to the stomach after passing through an opening in the diaphragm. The esophagus functions as a transport medium between compartments.\(^{54}\)

The stomach is a J shaped expanded bag, located just left of the midline between the esophagus and small intestine. The inner surface of the stomach is composed of longitudinal folding called rugae which allow the stomach to enlarge when food enters. The stomach capacity is up to 1.5 litres of material. The functions of stomach include storage of food, mechanical breakdown, absorption and digestion.\(^{55}\)
The duodenum lies between the upper and lower tracts. The duodenum is divided into four segments namely bulb, descending, horizontal, and ascending. The suspensory ligament attaches the superior border of the ascending duodenum to the diaphragm.  

**Lower gastrointestinal tract**

*Small Intestine*

The main function of the small intestine is to absorb proteins, lipids, and vitamins. It is approximately 6m in length, extending from the pyloric sphincter of the stomach to the ileo-caecal valve separating the ileum from the caecum. The small intestine consists of duodenum, jejunum and ileum.

The duodenum receives both pancreatic and bile juices. Here the digestive juices from the pancreas and the liver mix with hormones. The digestive enzymes break down proteins and bile and emulsify fats into micelles. The duodenum contains Brunner's glands which produce a mucus-rich alkaline secretion containing bicarbonate, which in combination with bicarbonate from the pancreas neutralizes HCl of the stomach.

Jejunum connects the duodenum to the ileum. It contains lining named plicae circulares and villi that increase the surface area of this part of the GI Tract. Sugars, amino acids, and fatty acids are absorbed into the blood here.

Ileum has villi similar to the jejunum, and absorbs mainly vitamin B12 and bile acids and any other remaining nutrients.
**Large Intestine**

The large intestine is horse-shoe shaped, length of approximately 1.5m and a width of 7.5cm and consists of the colon and rectum. The wall of the colon is made up of several haustra’s which are held under tension by taenia coli.

The colon connects to the rectum, and finally the anus. The main function of the large intestine is to absorb water. Other functions include accumulation of unabsorbed material to form faeces, digestion by bacteria, and reabsorption of salts, sugar and vitamins.

**Gastro-intestinal tract wall:**

The GI tract was can be divided into four layers as follows:

- Mucosa
- Submucosa
- Muscularis externa
- Serosa

**Mucosa**

It is the innermost layer of gastrointestinal tract. It is surrounding the lumen and directly contacts with chyme. The layer is made up of epithelium, lamina propria and muscularis mucosae.

**Submucosa**

The submucosa surrounds the muscularis mucosa and consists of connective tissue and larger vessels and nerves. At its outer margin there is a specialized nerve plexus called the submucosal plexus or Meissner plexus. This supplies the mucosa and submucosa.
**Muscularis externa**

The muscularis externa consists of an inner circular layer and an outer muscular layer. The circular muscle layer prevents food from traveling backward and the outer muscular layer shortens the tract. The coordinated contraction of these layers is called peristalsis. Food in the GI tract is called a bolus from the mouth down to the stomach. After the stomach, the food is partially digested and semi-liquid, and is referred to as chyme. In the large intestine the remaining semi-solid substance is referred to as faeces. Between the two muscle layers are the myenteric or Auerbach's plexus which controls peristalsis.

**Serosa**

This is the outermost layer of gastrointestinal tract. Stomach, initial part of duodenum, small intestine, colon and rectum are covered by serosa.
Table 1.2 Anatomy and Physiology Features of GIT

<table>
<thead>
<tr>
<th>Section</th>
<th>Length (cm)</th>
<th>Absorption mechanism</th>
<th>pH</th>
<th>Major constituents</th>
<th>Transit time of food (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>15-20</td>
<td>Passive diffusion, convective transport</td>
<td>5.2-6.8</td>
<td>Amylase, maltase, ptyalin, mucins</td>
<td>Short</td>
</tr>
<tr>
<td>Esophagus</td>
<td>25</td>
<td>-</td>
<td>5-6</td>
<td>-</td>
<td>Very short</td>
</tr>
<tr>
<td>Stomach</td>
<td>20</td>
<td>Passive diffusion, convective transport</td>
<td>1.2-3.5</td>
<td>HCl, pepsin, rennin, lipase, intrinsic factor</td>
<td>0.25-3.00</td>
</tr>
<tr>
<td>Duodenum</td>
<td>25</td>
<td>Passive diffusion, convective transport, Active transport, facilitated transport, ion pair pinocytosis</td>
<td>4.6-6.0</td>
<td>Bile, trypsin, chymotripsin, amylase, maltase, lipase, nuclease, CYP3A5</td>
<td>1-2</td>
</tr>
<tr>
<td>Jejunum</td>
<td>300</td>
<td>Passive diffusion, convective transport, active transport, facilitated transport</td>
<td>6.3-7.3</td>
<td>Amylase, maltase, lactase, sucrase, CYP3A5</td>
<td>-</td>
</tr>
<tr>
<td>Colon</td>
<td>150</td>
<td>Passive diffusion, convective transport</td>
<td>7.9-8.0</td>
<td>-</td>
<td>4-20</td>
</tr>
<tr>
<td>Rectum</td>
<td>15-19</td>
<td>Passive diffusion, convective transport, pinocytosis</td>
<td>7.5-8.0</td>
<td>-</td>
<td>Variable</td>
</tr>
</tbody>
</table>
ULCER AND ANTI-ULCER DRUGS:

Ulcers are defined as a distinct breach in the mucosa of the alimentary tract that extends through the muscularis mucosa into the submucosa or deeper.

Ulcers are to be distinguished from erosions, in which there is epithelial disruption within the mucosa but no breach of muscularis mucosa.

Peptic ulcers are chronic, lesions equal or greater than 0.5cm that occurs in any portion of the gastrointestinal tract exposed to the aggressive action of peptic juices/acid. Mostly peptic ulcer occurs in duodenum or stomach.62

Basic cause of Peptic Ulceration:

The basic cause of peptic ulceration includes high acid and peptic content, irritation, poor blood supply, infection by H.pylori by use of NSAID’s which inhibits the production of Prostaglandins and consequently decrease mucus and bicarbonate secretion. Smoking, drinking alcohol and radiation treatments also causes ulcer.63

Signs and symptoms

Symptoms of a peptic ulcer can be 64

- abdominal pain
- abdominal fullness
- nausea and vomiting
- blood vomiting
- foul-smelling of faeces due to oxidized iron from hemoglobin.
- heartburn
- weight loss
Diagnosis of ulcer

- Esophagogastroduodenoscopy (EGD, upper endoscopy, or gastroscopy)
- X-rays

Treatment

The various classes of drugs which are used as treatment aspects can be enlisted as follows

1. Reduction of gastric acid:
   a) H2 Anti Histamines: Cimetidine Ranitidine Pantaprazole
   b) Proton Pump Inhibitors: Omeprazole Lansoprazole, Pantoprazole, Rabeprazole
   c) Anti cholinergics: Pirenzapine Propantheline Oxyphenonium
   d) Prostaglandin Analogues: Misoprostil, Enprostil

2. Neutralization of gastric acid
   a) Systemic: Sodium bicarbonate
   b) Non-systemic: Magnesium hydroxide, magnesium trisilicate, aluminum hydroxide

3. Ulcer protective: Sucralfate Colloidal bismuth sub citrate

4. Ulcer Healing: Carbenoxolone sodium

5. Anti-H.pylori drugs: Amoxicillin, Clarithromycin, Metronidazole, Tetracycline

Prevention

- Avoid aspirin, ibuprofen, naproxen, and other NSAIDs. Try acetaminophen instead
- Avoid smoking or chewing tobacco
- Limit alcohol to not more than two drinks per day