1. Introduction:

The oral route plays an important role in the administration of drugs. It is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and absorb from these regions of the GIT depends upon the physicochemical properties of the drug, pharmaceutic factors and the patients related factors etc. It is a serious drawback in conditions where localized delivery of the drugs in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT. Dosage forms that deliver drugs into the colon rather than upper GIT prefers number of advantages. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Crohn's disease, carcinomas and infections) where by high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption.

1.1 Anatomy and physiology of colon

The colon forms the lower part of the gastrointestinal tract and extends from ileoceacal junction to the anus divided in to three parts colon, rectum and anal–canal. The colon is made up of caecum, the ascending colon, the hepatic flexure, the transverse colon, the splenic flexure, the descending colon, and the sigmoid colon. It is about 1.5 m long. The transverse colon is the lowest and the most mobile part with average diameter of about 65 cm. However, it varies in diameter from approx. 9.0 cm. in caecum to 2 cm in sigmoid colon. Unlike the small intestine, the colon does not have any villi but due the presence of plicae semilunares, which are crescentic folds, the intestinal surface of the colon is increased to 1300 c.m². The wall of colon is made of 4 layers, serosa, muscularis externa, sub mucosa, mucosa. The serosa is the exterior coat of the large intestine and consists of arioler tissue i.e. covered by single layer of squamous mesothelial cells. Muscularis externa is the major coat of the large intestine and is composed of an inner cerculer layer of fiber that surrounds the bowel and of the outer longitudinal layer. The submucosa is the layer of connective tissue that lies immediately beneath the mucosa. The mucosa is divided in to epithelium, lamina propria and muscularis mucosae. The muscularis mucosae consist of a layer of smooth muscle and separate the mucosa from the lamina propria.
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The activity in the colon can be divided into segmenting and propulsive movements. Segmenting movements by circular muscles cause the appearance of the sac-like haustra. The significant propulsive activity associated with defecation and effect by longitudinal muscles is less common and occurs an average of 3-4 times daily. Retrograde movements are common in the proximal portion of the colon and increase the retention of the material in the ascending colon and caecum. In the middle section of the colon, segmenting movements result in a slow progression of faeces towards the rectum, where as propulsive activity predominates in distal portion of colon.

![Anatomy of colon](image)

**Figure 1.1: Anatomy of colon**

1.1.1 Functions of colon

The colon serves four main functions, such as:

- Creation of a suitable environment for the growth of colonic microorganism such as Bacteriods, Eubacterium, Enterobacteriaceae.
- Storage reservoir of fecal contents.
- Expulsion of the contents of the colon at a suitable time.
- Absorption of water and electrolytes from the lumen, concentrating the fecal contents and secretion of $K^+$ and $HCO_3^-$. 

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Development of extended release dosage form of NSAIDs used in colon targeted drug delivery
1.1.2 pH of the colon
The pH of the gastrointestinal tract is subjected to inter/intra subject variation.

![The Human Digestive Tract pH Range Chart](image)

**Fig.1.2: The human digestive tract pH range chart**

1.1.3 Gastrointestinal transit
The gastric emptying of dosage form is highly variable and depends primarily on whether the subject is fed or fasted and the property of dosages form (such as size and density). The mean transit time from mouth to anus is 53.3hrs. The total mean colonic transit time is 25.0 hrs and is shorter in males than females. The transit time of small dosages form in GIT given in table 1.1.

**Table 1.1: Transit time of dosage form in GIT**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Transit time of dosage form in GIT (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>&lt;1 (fasting), &gt; 3 (fed)</td>
</tr>
<tr>
<td>Small intestine</td>
<td>3-4</td>
</tr>
<tr>
<td>Large intestine</td>
<td>20-30</td>
</tr>
</tbody>
</table>

1.1.4 Colonic micro-flora
A large number of anaerobic and aerobic bacteria are present throughout the entire length of human GIT. The concentration of bacteria in the human colon is $10^{11}$-$10^{12}$
CFU/ml (colony forming units/ml). The bacterial flora of colon is predominantly anaerobic and composed of more than 400 strains. The most important anaerobic bacteria are Bacteriodes, Bifidobacterium, Eubacterium, Eptococcus, Peptostreptococcus, Ruminococcus, Clostridium and Propionibacterium. The important facultative bacteria in large intestine are E.coli and lactobacillus. The principle source of nutrition for colonic microorganisms are carbohydrates, arriving in intestinal chime, including starch, non starch polysaccharides such as cellulose, hemi cellulose, guar gum, pectin, ispagola, sugar and oligosaccharides such as lactose, sorbitol and xylitol. It is evident that colonic bacterial population will have a significant impact, both negative and positive, on colonic drug delivery. The ability of selective metabolism of certain carbohydrates and anaerobic environment has been exploited in the development of delivery system. On the other hand, significant proteolytic activity has implication for delivery of peptides and protein drug.

1.2 Controlled Release Drug Delivery
The term “controlled release” is used to refer to a number of methods designed to modify the liberation of drug from a formulation. This terminology includes preparations labeled as “long acting,” “extended,” “delayed,” or “sustained release.” Controlled drug delivery systems have acquired a center stage in the arena of pharmaceutical R&D business. Such systems offer temporal and/or spatial control over the release of drug and grant a new lease on life to a drug molecule in terms of patentability. Controlled release drug delivery has been applied to new product development for more than 60 years. Over the past three decades, tremendous progress has been made in the development of theory, mathematical modelling, new rate controlling materials and technology platforms, as well as processing technologies. New and more sophisticated controlled release drug delivery systems are constantly being developed and tested. Successful fabrication of controlled release products is usually difficult and involves consideration of the physicochemical properties of the drug, pharmacokinetic behaviour of the drug, and route of administration, diseased state to be treated and most importantly placement of the drug in a dosage form that will provide the desired temporal and spatial delivery pattern for the drug.

In particular, the emergence of high performance polymers and aqueous based polymeric dispersions has made conventional processing technology more adaptable
to manufacture controlled release/ modified release dosage forms. Drug release modification is a technique or approach by which the delivery pattern of a therapeutic agent is altered via engineering of physical, chemical or biological components into delivery systems for achieving desired/ target plasma drug levels.

Modified release drug delivery systems are developed to modulate the apparent absorption or alter the site of release of drugs, in order to achieve specific clinical objectives that cannot be attained with conventional dosage forms. These systems cover a wide range of prolonged action formulation which provides continuous release of their active ingredients at a predetermined rate. The main objective of modified release drug delivery systems is to ensure safety and to improve efficacy of drugs as well as patient compliance. So they are designed to provide a therapeutic amount of drug on the specific site of absorption, and then to maintain the desired drug concentration.

Drug delivery or controlled release has been defined by Flynn as “the use of whatever means possible, be it chemical or mechanical, to regulate a drug’s access rate to the body’s central compartment, or in some cases, directly to the involved tissues”. It is well recognized that the introduction of Dextroamphetamine sulphate in 1952 and contact cold remedy in 1960 by Smithkline and French laboratories using their patented formula technology was historical milestone that motivated the further development of oral controlled release dosage form.

Controlled Drug Delivery (CDD) occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under and overdosing.

Polymers have been used as a main tool to control the drug release rate from the formulations. Extensive applications of polymers in drug delivery have been realized because polymers offer unique properties which so far have not been attained by any other materials. Polymers are becoming increasingly important in the field of drug delivery. Advances in polymer science have led to the development of several novel
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drug-delivery systems. New technological development in polymer-based encapsulations and controlled drug release systems offers possibilities for optimizing the administration of drugs. These improvements contribute to make medical treatment more efficient and to minimize side effects and other types of inconveniences for patients. Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Regular research is going on in field of use of natural occurring biocompatible polymeric material in designing of dosage form for oral controlled release administration.

1.2.1 Advantages of Controlled Drug Delivery System

**Reduced 'see-saw' fluctuation:**
Administration of a drug in a conventional dosage form [except via intravenous infusion at a constant rate] often results in 'see – saw' pattern of drug concentration in the systemic circulation and tissue compartments. The magnitudes of these fluctuations depend on drug kinetics such as the rate of absorption, distribution, elimination and dosing intervals. The 'see-saw' or 'peak and valley' pattern is more striking in case of drugs with biological half-lives of less than four hours, since prescribed dosing intervals are rarely less than four hours. A well designed controlled release drug delivery system can significantly reduce the frequency of drug dosing and also maintain a steadier drug concentration in blood circulation and target tissue cells.

**Patient Compliance:**
Lack of compliance is generally observed with long term treatment of chronic disease, as success of drug therapy depends upon the ability of patient to comply with the regimen. Patient compliance is affected by a combination of several factors, like awareness of disease process, patient faith in therapy, his understanding of the need to adhere to a strict treatment schedule. The problem of lack of patient compliance can be resolved to some extent by administering controlled release drug delivery system. Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction in personnel time to dispense, administer and monitor patients.

**Improved efficiency in treatment:**
Optimal therapy of a disease requires an efficient delivery of active drugs to the tissues, organs that need treatment. Very often doses far in excess to those required in the cells have to be administered in order to achieve the necessary therapeutically effective concentration. This unfortunately may lead to undesirable, toxicological and immunological effects in non-target tissue. A controlled release dosage forms leads to better management of the acute or chronic disease condition.

**Reduced total dose:**
Controlled release drug delivery systems have repeatedly been shown to use less amount of total drug to treat a diseased condition. By reducing the total amount of drug, decrease in systemic or local side effects are observed. This would also lead to greater economy.

### 1.2.2 Disadvantages of Controlled Drug Therapy

**Poor In- Vitro In- Vivo correlation:**
In controlled release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so called ‘Absorption window’ becomes important and may give rise to unsatisfactory drug absorption in vivo despite excellent in-vitro release characteristics.

**Patient Variation:**
The time period required for absorption of drug released from the dosage form may vary among individuals. Co-administration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patient.

**Dose dumping:**
Dose dumping is a phenomenon where by relatively large quantities of drug in a controlled release formulation is rapidly released, introducing potential toxic quantities of the drug into the systemic circulation. Dose dumping can lead to fatalities in case of potent drug, which have a narrow therapeutic index e.g. Phenobarbital.

**Less flexibility in accurate dose adjustment:**
In conventional dosage forms, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of controlled release dosage forms, this appears to be much more complicated. Controlled release property may get lost, if dosage form is fractured.
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Figure 1.3: Pharmacokinetic profile of different release patterns of various drug delivery systems

1.2.3 Fundamentals of Controlled Drug Delivery

The newer drug delivery systems are being investigated so as to alter the body distribution of drugs with a view to reduce the toxicity of drug or deliver them more efficiently to their site of action. There are a number of reasons for intense interest in development of drug delivery systems.

1. Possibility of repatenting existing drugs by applying the concepts and techniques of controlled drug delivery, coupled with almost prohibitively high cost of bringing new drug entities to market.

2. New systems are needed to deliver peptides, pharmacogenomics, hormones, vaccines and other proteins to their specific site if action without incurring significant immunogenicity or biological inactivation.

3. Therapeutic efficacy and safety profile of drugs can be improved by more precise spatial and temporal placements within the body compartment, thereby reducing both the quantity and number of doses.

However, in generalized way the controlled release systems are intended to exercise control on drug release in the body, whether this be of a temporal or spatial nature or both. In other words, the system attempts to regulate drug concentration within the tissue or cells.
The controlled delivery attempts to:-

- Sustain drug action at predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with a saw-tooth kinetic pattern.
- Localize drug action by spatial placement of a controlled release system adjacent to or in diseased tissue or organ.
- Targeted drug action by using carriers or chemical derivatives to deliver the drug to a particular target cell type.
- Provide a physiologically/therapeutically based drug delivery system. The amount and rate of drug release are determined by physiological/therapeutic needs of the body.

Idealistically, to maintain a constant drug level in either plasma or target tissue, release rate from a controlled release system should be equal to the elimination rate from plasma or target tissue. The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of therapeutically active moieties by using either polymer or by modifying parameters inherent in a selected route of administration. Polymeric drug carrier systems have been widely used to modify drug delivery.

Thus, the term controlled release implies a predictability and reproducibility in the drug release kinetics, which means that the release of drug ingredients from a controlled release drug delivery system proceeds at a rate profile that is not only predictable kinetically, but also reproducible from one unit to another. Recently, several technical advancements have been made. They have resulted in the development of new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the therapeutic activity, or targeting the delivery of drug to a tissue.

Significant clinical advances have been made over the last two decades in delivering therapeutic agents via a non-monotonic pattern at predetermined time intervals as a result of an improved understanding of relationship between clinical pharmacology, on the other hand, and bodily physiology and biological conditions, on the other. For example, many body functions and diseases follow a circadian rhythm (e.g., daily fluctuations of hormones, gastric secretion and emptying, bronchial asthma,
myocardial infarction, angina, rheumatic disease, ulcer, and hypertension). For example, Procardia XL is a zero-order release tablet of Nifedipine that not only reduces dosing frequency from t.i.d. to once daily, but also drastically improves the efficacy to safety ratio. Controlling the input rate results in gradual decrease in blood pressure, without the increase in heart rate and syncope associated with t.i.d. administration.

Methylphenidate is a compound indicated for attention deficit hyperactivity disorder without patent protection. Several new MR products of methylphenidate were introduced in 1990’s by different developers that offer clear clinical advantages over the products on the market (e.g. Ritalin, Ritalin SR). These products include a bimodal extended release tablet (Concerta), capsule (Metadate CD), and a pulsatile release capsule (Ritalin LA), all of them were designed to produce fluctuation of blood levels over time to overcome acute tolerance associated with constant rate of delivery, thus enabling dosing convenience of this controlled drug for school children. As a result, modified release dosage form development has been an important tool of product line extension and an integral part of product life cycle management strategy.

1.2.4 Basic Kinetics of Controlled Drug Delivery

In order to establish a basis for discussion of the influence of drug properties and the route of administration on controlled drug delivery, following mechanisms need a fair mention, behaviour of drug within its delivery systems and the behaviour of the drug and its delivery system together in the body. The first of the two elements basically deals with the inherent properties of drug molecules, which influence its release from the delivery system. However, in sustained/controlled release product, the release of drug from the dosage form is the rate limiting step; thus, drug availability is controlled by the kinetics of Drug release than absorption. Various approaches, like dissolution, diffusion, swelling, osmotic pressure, complexation, ion exchange and magnetic field can be utilized for preparing a controlled release system of a drug. The second element, the behaviour of the drug and its delivery system in the body, is extremely complex involving the fate of drug during transit to target site as well as its fate while in the bio media. Availability of drug to its target generally depends on its pharmacokinetics as well as the carrier. In case of drug targeting the carrier alters the pharmacokinetics of drug in the body. The influence of physiological constraints on
the fate of delivery system in the body is usually negative, for example oral absorption is usually limited by gastrointestinal transit time of the delivery system. The duration of a drug after oral administration is mainly a function of drug related properties such as rate of absorption and clearance as well as residence times of the delivery systems at absorption site.

1.3 Oral Controlled Drug Delivery

For controlled release systems, the oral route of administration has received the most attention. This is because there is more flexibility in dosage form for the oral route than there is for parenteral route. Patient acceptability is quite high. Oral route is most convenient, safe, widely accepted means of administering drugs. The number of oral controlled drug delivery systems on pharmacy shelves has increased exponentially during the last decade, and this growth is expected to continue into foreseeable future. The design objective for modifying oral drug release is to alter the rate of drug input (dissolution/absorption) in the intestinal lumen to achieve a predetermined plasma profile.

1.3.1 Multiple drivers for this high growth rate include the following:

- **Convenience and Compliance:**
  Modified release products that reduce dosing frequency provide convenience that can have a positive impact on patient adherence and outcomes.

- **Reduced health care costs:**
  Increased patient compliance is appealing to third party payers because of potential to reduce overall health care costs.

- **Unmet medical needs:**
  Management of some diseases that have historically been difficult to treat is now possible because a drug can be delivered to the right site at right time in the right amount.

- **Market exclusivity:**
  Modified release drug delivery system provide market exclusivity and extend a products life cycle, which is of commercial interest to pharmaceutical firms and promote product innovation.
Large scale manufacturing:
Scientific and technology advancement have made it possible to develop more intricate delivery systems and manufacturing them on a large scale (14).

1.3.2 Disadvantages

1. Difficulty or impossibility of quick stoppage of pharmacological action of drug when serious posing occurs.
2. Reproducibility of action affected by rate of gastric emptying.
3. Little or no efficacy of pharmaceutical dosage forms if drug is not absorbed by the intestinal mucosa.
4. Difficulty of adjusting posology to several inters individual pharmacokinetics.
5. Rate release dependent of pharmaceutical dosage form integrity.
6. Low bioavailability in some cases and large size of pharmaceutical dosage leads to increase in cost.

The development of a pharmaceutical product for delivery irrespective of its physical form (solid/liquid/semisolid), involve varying extends of optimizations of dosage form characteristics with in the inherent constraints of gastrointestinal physiology. In the exploration of oral controlled release drug administration, one encounters three areas of potential challenge.

➢ Development of a drug delivery system:
To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment.

➢ Modulation of gastro intestinal transit time:
To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for prolonged period of time to maximize the delivery of a drug dose.

➢ Minimization of hepatic first pass elimination:
If the drug to be delivered is subjected to extensive hepatic first pass elimination, preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.
1.3.3 Common modes of Oral Modified Release delivery include:

1.3.3.1 Delayed Release:
This is a specific type of modified release form that releases a drug at a time other than promptly after administration e.g. an enteric coating. 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 e.g. delayed release system include repeat action tablets/ capsules, enteric coated tablets, where timed release is achieved by carrier coating. Asacol and Lialda are delayed release tablets designed to release mesalamine in the distal ileum and/or colon for ulcerative colitis treatment, while Pentasa is an extended release capsule that delivers the same active throughout the gastrointestinal system. Materials that have been to oral medication of enteric release mainly comprise of:

a. Shellac and Zein of natural sources
b. Derivatives of cellulose and methacrylic acid copolymers containing carboxylic functional groups. Presently, synthetic and semisynthetic polymers are most preferred system for enteric film coating of particles e.g. of pH-dependent polymers include cellulose acetate phthalate (CAP), hydroxyl propyl methylcellulose phthalate (HPMCP), methacrylic acid and methacrylic esters.

1.3.3.2 Site-specific or Timed Release targeting:
It refers to targeting of a drug directly to a certain biological location. e.g. for colonic delivery. In the case of site-specific release, the target is adjacent to or in diseased organ or tissue for receptor release; the target is the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspect of drug delivery and are also considered as controlled drug delivery systems. The optimal colon-specific drug delivery includes use of pH sensitive or slow eroding polymers, swelling or osmotic controlled systems for timed release. Certain plant polysaccharides (such as amylose, pectin, and guar gum), pH sensitive hydrogels, and microbially degradable polymers especially azo cross linked polymers have also been studied for targeting drugs to colon.

1.3.3.3 Sustained release systems:
The term sustained release is known to have existed in the medical and pharmaceutical literature for many decades. Sustain release has been constantly used to retard the release of therapeutic agent such that its appearance in the circulation is delayed and/or prolonged and its plasma profile is sustained in duration. The onset of
its pharmacological action is often delayed and duration of therapeutic action is sustained. The onset of its pharmacological action is often delayed, and the duration of its therapeutic effect is sustained. The object of sustain release of drug, in a general way is to modify the normal behaviour of drug molecule in a physiological environment. It can lead to the following:

- Sustaining drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with minimization of desirable side effects.
- Localization of drug action by spatial placement of a controlled release system usually rate controlled adjacent to or in the diseased tissue of organ.
- Targeting drug action by using carriers of chemical derivatives to deliver drug to particular target cell type.

**1.3.3.4 Extended Release Systems:**

Extended release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing drug over an extended period of time after administration of a single dose. Extended release dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate release dosage forms. The release can be a zero-order, first-order or biphasic release. The term controlled release, prolonged action, and sustained releases are used synonymously with extended release. USP uses the term to describe a formulation that does not release active substance immediately after oral dosing and that also allow a reduction in dosing frequency. Since the release from a controlled release dosage form is dependent on release of drug from dosage form therefore the drug release pattern is more uniform and approaches the desired zero order release rate, in contrast to the conventional immediate release formulations where drug release is more fluctuating and is need for frequent dosing to maintain the desired drug level in the body. Some drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. When conventional immediate release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys associated with the taking of each dose. However, when doses are not administered on schedule, the resulting peaks and valley reflect less than optimum drug therapy.

It is desirable to maintain a therapeutic blood concentration in order to achieve the desirable pharmacological effects. To maintain a narrow range of therapeutic blood
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concentration it is desirable to have a dosage form that can deliver the drug in a more sustainable or controlled way to achieve the desired results. Extended release tablets and capsules are commonly taken once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended release products provide an immediate release of drugs that promptly produces the desired therapeutic effect, followed by gradual release of additional amount of drugs to maintain this effect over a predetermined period. The sustained plasma drug levels provided by extended release products often eliminate the need for night dosing, which benefits not only the patient but the caregiver as well.

1.3.3.5 Characteristics that make a drug suitable for Extended Release formulation:

- **Drug is administered in relatively small doses:**
  The need for large single doses would lead to dosage units too large for the patient to swallow.

- **The drug doesn’t exhibit a very slow rate of elimination:**
  A drug with a slow rate of elimination has a long elimination half-life and hence is naturally long acting. Therefore, extended release forms are not necessary. A drug with elimination half-life of 2-4 hrs is ideal.

- **The drug possesses a good margin of safety:**
  Dose dumping such as with patient misuse (e.g. chewing of tablet) can result in high drug levels that make toxic.

- **Drug is used in treatment of chronic conditions:**
  To ensure patient adherence prescribed regimens, an extended release form is taken once/twice daily. This is convenient for patients who require long term treatment for chronic conditions.

- **The drug has appropriate molecular size, good solubility and lipophilicity:**
  The drug should be absorbed by passive diffusion and the absorption should not be dependent on drug solubility.

1.3.3.6 Programmed Release:

It includes pulsatile, delayed extended release. Pulsatile delivery generally refers to release of a portion of the total payload in a burst, followed by periods of little or no release (lag phase) in a defined temporal pattern. The first pulsed delivery formulation
that released the active substance at a precisely defined time point was developed in the early 1990s. In this context, the aim of the research was to achieve a so-called sigmoidal release pattern for e.g. Ritalin LA capsule is a pulsatile delivery system that provides immediate release of 50% of total dose upon oral ingestion, followed by a burst release of remaining drug after 4 hours. The fundamental system design of pulsatile release is based on combination of a range of formulation approaches, including single or multiple unit immediate release and delayed release systems.
Pulsatile systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastro-intestinal motility, etc. These time-controlled systems can be classified as single unit (e.g. tablet or capsule) or multiple unit (e.g. pellets) systems. By timing the administration of a programmed release device, therapeutic plasma concentration can be obtained at a particular time to counter the diurnal nature of certain diseases, such as angina, hypertension, asthmatic attacks or stiffness of arthritic patients during early morning hours, and heart attack at night.

1.3.4 Factors Influencing the Design and Performance of Sustained or Controlled Release Products

1.3.4.1 Drug Properties
The physicochemical properties of a drug include stability, solubility, partitioning characteristics, charge and protein binding; play a dominant role in the design and performance of controlled release systems. The design of controlled release delivery system is subject to several variables of considerable importance. Among these are the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy, and the properties of the drug. Each of these variables is interrelated, and this imposes certain constraints upon choices of route of delivery, the design of delivery system, and the length of therapy.

**Partition coefficient:**
Ideally, the release of an ionisable drug from a controlled release system should be programmed in accordance with the variation in pH of the different segments of gastrointestinal tract so that the amount of preferentially absorbed species and thus the plasma level of drug will be approximately constant throughout the, time course of drug action. Between the time that a drug is administered and the time it is eliminated from the body it must diffuse through a variety of biological membranes that act
primarily as a lipid like barrier. A major criterion in evaluation of a drug to penetrate these lipid membranes is its apparent oil/water partition coefficient (K), defined as:

$$K = \frac{C_o}{C_w}$$  - (1)

Where, Co is the equilibrium concentration of all forms of the drug, e.g., ionized and unionized, in an organic phase at equilibrium, and Cw is the equilibrium concentration of all forms in aqueous phase. In general, drugs with extremely large values of K are very oil soluble and will partition into membranes quite readily. The more effectively a drug crosses membrane the greater its activity.

**Drug stability:**

Drug stability of importance for oral dosage forms is the loss of drug through acid hydrolysis and/or metabolism in the GI tract. Since a drug undergoes degradation at a much slower rate than a drug in suspension or solution, it would seem to improve significantly the relative bioavailability of a drug that is unstable in the GI tract by placing it in a slowly available controlled release form. For those drugs that are unstable in stomach, the most appropriate controlling unit would be the one that releases its contents only in the intestine.

**Protein binding:**

Distribution of a drug into the extra vascular space is governed by equilibrium process of dissociation of drug from the protein. The drug-protein complex can serve therefore as a reservoir in the vascular space for controlled drug release to extravascular tissues, but only for those drugs that exhibit a high degree of binding. Thus the protein binding characteristics of a drug can play a significant role in its therapeutic effect, regardless of the type of dosage form. Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for the drug and such drugs generally do not require a controlled release dosage form.

**Molecular size and diffusivity:**

A drug must diffuse through a variety of biological membranes, drugs in many controlled release systems must diffuse through a rate controlling membrane or matrix. The ability of a drug to diffuse through membranes, it’s so called diffusivity (diffusion coefficient) is a function of its molecular size.
1.3.4.2 Biological properties

The biological properties of a drug are a function of its physicochemical properties. Typical pharmacokinetic studies on absorption, distribution, metabolism and excretion characteristics of a drug and those resulting from pharmacological studies will be considered as physicochemical properties.

- **Absorption:**
  The rate and extent and uniformity of absorption of a drug are important factors when considering its formulation into a controlled release system. The rate limiting step in drug delivery from a controlled release system is its release from a dosage form, rather than absorption. This becomes most critical in the case of oral administration. Slowly absorbed drugs will be difficult to formulate into controlled release systems. The extent and uniformity of the absorption of a drug, as reflected by its bioavailability and the fraction of total drug absorbed, may be quite low for a variety of reasons. This is usually not a prohibitive factor in its formulation into a controlled release system. Some possible reasons for a low extent of absorption are poor water solubility, low partition coefficient, acid hydrolysis, metabolism or site specific absorption. These problems can be overcome by an appropriately designed controlled release system.

- **Distribution:**
  The distribution of a drug into vascular and extravascular spaces in the body is an important factor in its overall elimination kinetics. This influences the formulation of that drug into a controlled release system, primarily by restricting the immediate elimination of the drug and the dose size that can be employed. Two parameters that are used to describe the distribution characteristics of a drug are apparent volume of distribution ($V_d$) and rate of drug concentration in tissue. The apparent volume of distribution is a proportionality constant that relates drug concentration in the blood or plasma to the total amount of drug in body.

- **Metabolism:**
  The metabolic conversion of a drug to another chemical form usually can be considered in the design of a controlled system for that drug. As long as the location, rate, and extent of metabolism are known and the rate constant for the process are not too large, successful controlled release products can be developed.
There are two factors associated with metabolism of some drugs, however that presents problem for their use in controlled release systems; first is the ability of the drug to induce or inhibit enzyme synthesis, this may result in fluctuating drug blood level due to intestinal metabolism and second is the hepatic first pass effect.

- **Elimination and biological half-life:**

  The rate of elimination of a drug is described quantitatively by its biological half-life. A drug with a short half-life requires frequent dosing, and this makes it a desirable candidate for a controlled release formulation. On the other hand, a drug with a long half-life is dosed at greater time intervals, and thus there is less need for a controlled release system. A drug with a half-life of less than 2 hrs probably should not be used, since such systems will require unacceptably large release rates and large doses. At the other extreme, a drug with a half-life greater than 8 hrs also probably should not be used.

- **Dose size:**

  Since a controlled release system is designed to alleviate repetitive dosing, it naturally will contain a greater amount of drug than a corresponding conventional form. For those drugs requiring large conventional doses, the volume of sustained dose may be so large as to be impractical, depending on route of administration. The same may be true of drugs that require a large release rate from the controlled release system, e.g. drugs with short half-lives. For the oral route, the volume of product is limited by patient acceptance.

- **Route of drug delivery:**

  The area of the body in which drugs will be applied or administered can be restrictive on the basis of technological achievement of a suitable controlled release mechanism. At times, the drug delivery systems, in certain route of administration, can exert a negative influence on drug efficacy, particularly during chronic administration; hence other routes of administration should be considered. Performance of the controlled release systems may also be influenced by physiological constraints imposed by particular route, such as first pass metabolism, gastrointestinal motility, blood supply and sequestration of small foreign particle by liver and spleen.

- **Target site:**

  In order to minimize unwanted side effects, it is desirable to maximize the fraction of applied dose reaching the target organ or tissue. This can be partially achieved by local administration or by use of carriers. However the absorptive surfaces of most
routes are impermeable to macromolecules or other targeted delivery systems, thereby necessitating either intravascular or intra-arterial administration.

➢ The patient:
Whether the patient is ambulatory or bedridden, young or old, obese or gaunt, etc. can influence the design of a controlled release product. The main objective of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. That is, the drug delivery systems should deliver drug at the rate dictated by the needs of the body over a specified period of treatment.

1.4 Approaches to Achieve Controlled Release Drug Delivery

Various techniques have been used in the formulation of controlled release products. In general, controlled release formulations can be divided into different categories based on the mechanism of drug release.

1.4.1 Ion exchange resins

It is based on the formation of drug resin complex formed when an ionic solution is kept in contact with ionic resins. The drug from these complexes gets exchanged in gastrointestinal tract and released with excess of Na+ and Cl- present in gastrointestinal tract. These systems generally utilize resin compounds of water insoluble cross-linked polymer. They contain salt forming functional group in repeating positions on the polymer chain. The rate of drug diffusion out of the resin is controlled by the area of diffusion, diffusional path length and rigidity of the resin which is function of the amount of cross linking agent used to prepare resins. The release rate can be further controlled by coating the drug resin complex by microencapsulation process. The resins used include Amberlite Indion, polyesterol resins and others. Ion exchange resins are cross-linked water-insoluble polymers carrying ionisable functional groups. The resins have been used in various pharmaceutical applications, primarily for taste masking and controlled release systems. In tablet formulations, ion exchange resins have been used as disintegrants because of their swelling ability. It forms irreversible complex with ionizable drugs upon prolonged exposure of the drug to the resin. A resin bound-drug is removed when appropriate ions are in contact with ion-exchanged groups. The area and length
of diffusion pathway and the amount of cross-linked polymer in the resin moiety
governs the rate of drug release. Sriwogjanya investigated the effect of ion exchange
resins as release modifiers in matrix formulations containing oppositely charged drugs
and they concluded that addition of ion exchange resins to HPMC-matrices
significantly modified the release of oppositely charged drug molecules, because a
complex formed between the drug and resin retarded the drug release.

1.4.2  Dissolution controlled release

This type of controlled release involves two processes, the detachment of drug
molecules from the surface of their solid structure to the adjacent liquid interface,
followed by their diffusion from the interface into the bulk liquid medium. The rate of
dissolution and the amount dissolved per unit of time from this system can be
calculated using Noyes-Whitney equation (1897). The rate of dissolution is described
by the Noyes-Whitney equation as shown below:

\[
\frac{dW}{dt} = \frac{DA(C_s - C)}{L}
\]

Where:

- dW/dt is the rate of dissolution
- A is the surface area of the solid
- C is the concentration of the solid in the bulk dissolution medium
- C_s is the concentration of the solid in the diffusion layer surrounding the solid
- D is the diffusion coefficient
- L is the diffusion layer thickness
1.4.3 Diffusion controlled release

Robinson, 1987, reported that, diffusion systems are characterized by the release rate of a drug being dependent on its diffusion through an inert membrane barrier. Usually this barrier is an insoluble polymer. The drug release in this type of systems is controlled by diffusion of drug out of the matrix. Various physical and chemical approaches have been successfully applied to produce well characterized delivery systems that extend drug input into g.i.t with in the specifications of the desired release profile. Today, most proprietary and non-proprietary Extended Release technologies are based on polymeric systems.

1.5 Extended Release Oral solid products fall into one of three broad categories:

- Reservoir System
- Osmotic System
- Matrix System

1.5.1 Reservoir Polymeric Systems

A typical reservoir system consist of a core containing solid drug or highly concentrated drug solution surrounded by a film or membrane of a rate controlling material as shown in fig.1.5. In this design, the only structure effectively limiting the release of the drug is the polymer layer surrounding the reservoir. Based on Fick’s first law of diffusion, one dimensional release rate of a drug from a reservoir system at steady state is given by:
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dQ/dt = \frac{DAK}{L} \times C

Where

- \( Q \) is the total amount of drug released at time \( t \)
- \( D \) is the diffusion coefficient of the drug
- \( A \) is effective membrane surface area for drug diffusion
- \( K \) is partition coefficient of drug between the barrier membrane and external aqueous phases.
- \( L \) is diffusional path length
- \( C \) is the drug concentration gradient between the solubility, \( C_s \), in the reservoir and the drug concentration, \( C_e \), in the external aqueous medium.

The membrane coating is essentially uniform in composition and thickness, for a given molecule and system composition, \( D, A, K, L \) and \( \Delta C \) are constant in equation under sink conditions (\( C_s >> C_e \)). Thus the amount of drug released as a function of time can be obtained by integration:

\[ Qt = DAK \frac{\Delta C}{L} \times t = kt \]

\( k \) is the release rate constant. The driving force of such systems is the concentration gradient of active molecules between reservoir and sink. Thus, the drug releases from this type of system follows apparent zero order kinetics until \( \Delta C \) is no longer constant, due to complete dissolution of solid drug in the core. It is applicable to soluble drugs because the reservoir system relies on \( \Delta C \) as the driving force for drug diffusion. For insoluble drugs, the values of \( C_s \) may be too low to render adequate driving force, resulting in over-attenuated and incomplete drug release.

Drug release from a reservoir system usually varies with pH, unless the solubility of the active is pH-independent. To achieve pH-independent release for drugs with pH-dependent solubility, \( C_s \) in the core needs to remain unchanged. Success with Incorporating of buffering agents to maintain constant pH in the core has been reported. Commercial products based on Reservoir Drug Delivery System are mentioned in Table 1.2. In developing oral products based on ER reservoir
technology, polymer film coated beads or tablets and microencapsulates (microparticles, microspheres or nanoparticles) are common dosage form presentations. Aqueous dispersions are applied mostly as drug release barrier include Ammoniomethacrylate copolymers (Eudragit RL, 30D, RS30D), Methacrylic ester copolymers (Eudragit, NE30D, polyvinyl acetate aqueous dispersion (kollicoat SR 30D).

![Figure 1.5: Reservoir drug delivery system](image)

Table 1.2 – Commercial products based on Reservoir Drug Delivery System

<table>
<thead>
<tr>
<th>Products</th>
<th>Active ingredient</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nico-400</td>
<td>Nicotinic acid</td>
<td>Jones</td>
</tr>
<tr>
<td>Nitrospan capsules</td>
<td>Nitroglycerin</td>
<td>Rorer</td>
</tr>
<tr>
<td>Cerespan capsules</td>
<td>PapaverinHCl</td>
<td>Rorer</td>
</tr>
<tr>
<td>Histapan capsules</td>
<td>Chlorpheniramine maleate</td>
<td>Rhone-Poulenc Rorer</td>
</tr>
<tr>
<td>Measurin tablets</td>
<td>Acetylsalicylic acid</td>
<td>Sanofi-Winthrop</td>
</tr>
<tr>
<td>Bronkodyl capsule</td>
<td>Theophylline</td>
<td>Winthrop</td>
</tr>
</tbody>
</table>

**1.5.1.1 Advantages**

- Zero order delivery is possible.
- Release rate variable with polymer type.
1.5.1.2 Disadvantages

- System must be physically removed from implant sites.
- Difficult to deliver high molecular weight compounds.
- Potential toxicity if system fails.

![Drug Release from a Typical Reservoir System]

**Figure 1.6: Drug Release from a Typical Reservoir System**

1.5.2 Osmotic Pump System:

It is similar to a reservoir device, but contains an osmotic agent that acts to imbibe water from surrounding medium via a semipermeable membrane. Such a device called elementary osmotic pump was first described by Higuchi in 1975. The delivery of active agent from the device is controlled by water influx across the semipermeable membrane. The drug is forced out of an orifice in the device by the osmotic pressure generated within the device. The size of the orifice is designed to minimize solute diffusion, while preventing the build-up of hydrostatic pressure head that has the effect of decreasing the osmotic pressure and changing the volume of the device. Drug release from this system is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the property of drug and system. Some of the commercially marketed oral osmotic drug delivery products are listed in Table 1.3. In developing oral products, two types of osmotic pump systems have frequently used, a one-chamber EOP system (fig. 1.7), e.g., Push-Pull and Push-Stick.
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Fig. 1.7: Representation of Elementary Osmotic Pump

Table 1.3: List of Commercially Marketed Oral Osmotic Drug Delivery Products

<table>
<thead>
<tr>
<th>Product name</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acutrim</td>
<td>Phenylpropranolamine</td>
</tr>
<tr>
<td>Alpress</td>
<td>LP Prazosin</td>
</tr>
<tr>
<td>Calan SR</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Cardura XL</td>
<td>Doxazocinmesylate</td>
</tr>
<tr>
<td>Concenta</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>Efidac 24</td>
<td>Pseudoephidrine</td>
</tr>
<tr>
<td>Glucotrol XL</td>
<td>Glipizide</td>
</tr>
</tbody>
</table>

Materials used osmotic pump systems: Cellulose acetate is the most commonly used polymer that constitutes the semipermeable membrane of an osmotic pump device. Other polymers used are cellulose butyrate, polyurethane, ethyl cellulose, PEG, PVC, and PVA. Osmotic agents such as sodium chloride are another key ingredient of an osmotic system.

1.5.2.1 Advantages:
Zero order release rates are obtainable. Reformulation is not required for different drugs. Release of drug is independent on the environment of the system.
1.5.2.2 Disadvantages:
System can be much more expensive than conventional counterparts. Quality control is more extensive than most conventional tablets.

1.5.3 Matrix Systems:

Historically, the most popular drug delivery systems have been the matrix because of its low cost and ease of fabrication. Methods of altering the kinetics of drug release from the inherent first order behaviour especially to achieve a constant rate of drug release from matrix devices have involved several factors.

Requirements of matrix materials:

- They must be completely inert and non-reactive with the drug and additives in the tablet.
- They must be able to form stable and strong matrices when compressed either directly or more often as granules prepared by the addition of a binding agent.
- They must be non-toxic.

In a matrix system, the drug substance is homogeneously mixed into a rate controlling material and other active ingredients as a crystalline, amorphous or molecular dispersion. Technical advancements in area of matrix formulation made controlled release products development much easier than before and improved upon the flexibility of delivering a wide variety of drugs with different physicochemical and biopharmaceutical properties. Matrix technologies have often proven popular among the oral controlled drug delivery technologies because simplicity, ease of manufacturing, high level of reproducibility, stability of raw materials and dosage form and ease of scale up and process validation. This is reflected by the large number of patents filed each year and by the commercial success of a number of novel drug delivery systems based on matrix technologies. Matrix-based delivery technologies have steadily matured from delivering drugs by first-order or square-root-of-time release kinetics to much more complex and customized release patterns. In order to achieve linear or zero-order release, various strategies that seek to manipulate tablet geometry, polymer variables, and formulation aspects have been applied. Various drug, polymer, and formulation-related factors, which influence the \textit{in situ} formation
of a polymeric gel layer/drug depletion zone and its characteristics as a function of time, determine the drug release from matrix systems.

Various mathematical models, ranging from simple empirical or semi-empirical (Higuchi equation, Power law) to more complex mechanistic theories that consider diffusion, swelling, and dissolution processes simultaneously, have been developed to describe the mass transport processes involved in matrix-based drug release.

1.5.3.1 Classification of Matrix Tablets

1.5.3.1.1 On the Basis of Porosity of Matrix:

Matrix system can also be classified according to their porosity (30) and consequently, macro porous; micro porous and non-porous systems can be identified:

- **Macro porous Systems:** In such systems the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 µm. This pore size is larger than diffusant molecule size.

- **Micro porous System:** Diffusion in this type of system occurs essentially through pores. For micro porous systems, pore size ranges between 50 – 200 Å, which is slightly larger than diffusant molecules size.

- **Non-porous System:** Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

1.5.3.1.2 On the Basis of Retardant Material Used:

- **Lipid Matrices:**
  These matrices prepared by the lipid waxes and related materials. Drug release from such matrices occurs through both pore diffusion and erosion. Release characteristics are therefore more sensitive to digestive fluid composition than to totally insoluble polymer matrix. Carnauba wax in combination with stearl alcohol or stearic acid has been utilized for retardant base for many sustained release formulation.

- **Biodegradable Matrices:**
  These consist of the polymers which comprised of monomers linked to one another through functional groups and have unstable linkage in the backbone. They are biologically degraded or eroded by enzymes generated by surrounding living cells or
by nonenzymatic process into oligomers and monomers that can be metabolised or excreted. Examples are natural polymers such as proteins and polysaccharides; modified natural polymers; synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

**Mineral Matrices:**

These consist of polymers which are obtained from various species of seaweeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaeophyceae) by the use of dilute alkali.

**Hydrophilic Matrices:**

It refers to a matrix system in which rate controlling materials are water soluble or swellable. It is polymer based drug delivery system in which two competing mechanisms are involved in the drug release: Fickian diffusional release and relaxational release. The primary rate controlling materials are polymers that hydrate and swell rapidly in an aqueous medium, and form a gel layer on the surface of the system. Diffusion across the viscous gel layer is not the only drug release pathway, as erosion of the matrix following polymer relaxation also contributes to the overall release. The relative contribution of each component to total release is primarily dependent on properties of a given drug and matrix composition.

The release of a sparingly soluble drug from hydrophilic matrices involves the simultaneous ingress of water and desorption of drug via a swelling-controlled diffusion mechanism. As water penetrates into a glassy matrix and lowers the polymer glass transition temperature, the polymer swells, slowly disentangles, and eventually dissolves, releasing the undissolved drug.

A semi-empirical exponent equation that was introduced in 1980 has been widely used to describe drug release behaviour from hydrophilic matrix systems:-

\[ Q = k t^n \]

Where

\( Q \) = fraction of drug released in time

\( K \) = rate constant incorporating characteristics of the macromolecular network system and the drug

\( n \) = diffusional exponent
It has been shown that value of n is indicative of drug release mechanism. For n=0.5, drug release follows a Fickian diffusion mechanism which is driven by a chemical potential gradient. For n=1, drug release occurs via relaxational transport, which is associated with stresses and phase transition in hydrated polymers. For 1>n>0.5, non-fickian diffusion behaviour is observed as a result of contributions from diffusion and polymer erosion.

Commonly available polymers for hydrophilic matrices include:

- Non-ionic soluble cellulose ethers, such as HPMC, HPC, HEC with varying degrees of substitutions and viscosity grades.
- Water soluble natural gums of polysaccharide of natural origin, such as xanthan gum, alginate and locust bean gum.
- Polyvinyl acetate and povidone mixtures
- Ionic methacrylate copolymers (Eudragit L30D, FS 30D) etc.

![Matrix Diffusional System](image)

**Figure 1.8: Matrix Diffusional System**

**Table 1.4: Matrix Dissolution Products**

<table>
<thead>
<tr>
<th>Products</th>
<th>Active Ingredient</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extentab tablets</td>
<td>-</td>
<td>Whitehall Robins</td>
</tr>
<tr>
<td>Mestinon</td>
<td>Pyridostigmine bromide</td>
<td>ICN</td>
</tr>
<tr>
<td>Demazin</td>
<td>Dexchlorpheniramine maleate</td>
<td>-</td>
</tr>
<tr>
<td>Chlor-Trimiton</td>
<td>Chlorpheniramine maleate</td>
<td>-</td>
</tr>
</tbody>
</table>
Hydrophobic Matrix Systems:
The hydrophobic matrix system was the earliest oral extended release platform for medicinal use. In fact, its prototypes can be traced back to the second century BC and fourth century AD, when animal fats and wax pills were used to prolong the medicinal effects of Chinese medicines. For example, medical practitioners were instructed to “use wax pills for their resistance to dissolve thereby achieving the effect gradually and slowly.” In modern medicine, the matrix technology has been successfully applied to many commercial products for many decades. For e.g., Premarin tablets, one of the classic examples, have been on market since 1942. This is the only system where the use of polymer is not essential to provide controlled drug release, although insoluble polymers have been used. As the term suggests, the primary rate-controlling components of hydrophobic matrix are water insoluble in nature. These ingredients include waxes, glycerides, fatty acids, and polymeric materials such as ethyl cellulose, methyl cellulose and acrylate copolymer. To modulate drug release, it may be necessary to incorporate soluble ingredients such as lactose into formulation. The presence of insoluble ingredient in the formulations helps to maintain the physical dimension of hydrophobic matrix during drug release. As such, diffusion of active ingredient from the system is the release mechanism and the corresponding release characteristic can be described by Higuchi equation known as square root of time release kinetic. The square root of time release profile is expected with a porous monolith, where the release from such system is proportional to the drug loading. In addition, hydrophobic matrix systems generally are not suitable for insoluble drug because the concentration gradient is too low to render adequate drug release. As such, depending on actual ingredient properties or formulation design, incomplete drug release within the gastrointestinal transit time is a potential risk and need to be delineated during the development. With the growing needs for optimization of therapy, matrix systems providing programmable rates of delivery become more important. Constant rate delivery always has been one of the primary targets of controlled release system especially for drug with narrow therapeutic index. In a hydrophobic inert matrix system, this involves essentially negligible increase of the device surface or change in dimension. For a homogeneous monolithic matrix system, the release behaviour can be described by Higuchi equation, subject to the matrix-boundary conditions:
\[ Q_t = \sqrt{\frac{D C_s (2A-C_s t)}{t}} \]

Where:

\( Q_t \) is the drug released per unit area at time \( t \)

\( A \) is the drug loading per unit volume

\( C_s \) is drug solubility

\( D \) is the diffusion coefficient in the matrix phase

Equation 1 was derived based on the assumption that

1. Pseudo steady state exists
2. The drug particles are small compared to the average distance of diffusion
3. The diffusion coefficient is constant
4. Perfect sink conditions exist in the external media
5. Only the diffusion processes occurs
6. The drug concentration in the matrix is greater than the drug solubility in polymer
7. No interaction between drug and matrix takes place

a. In case of \( A >> C_s \) eqn. 1 reduces to

\[ Q_t = \sqrt{2DAC_st} \]  

Thus the amount released is proportional to the square root of time \( A, D, \) and \( C_s \).

Drug release from a porous monolithic matrix system involves the simultaneous penetration of surrounding liquid, dissolution of the drug and leaching out of the drug through intestinal channels or pores. The volume or length of the openings in the matrix must be accounted for in the diffusion equation leading to a second form of the Higuchi equation:

\[ Q_t = \sqrt{\frac{e C_s (2A-eC_s D_a/T.t)}{t}} \]

\( e \) is porosity of matrix, \( T \) is tortuosity of matrix.

Tortuosity is introduced to account for an increase in diffusion path length, due to branching and bending of pores. Porosity is the fraction of matrix that exists as pores or channels, into which the surroundings liquid can ingress. It is the total porosity of the matrix after the drug has been extracted. The total porosity consists of initial
porosity due to air or void space in the matrix before the leaching process begins, the
porosity created by extracting the drug and the water soluble excipients. When no
water soluble excipient is present in the matrix and the initial porosity is smaller than
the porosity. With a porous monolith a square root of time release profile is expected.
In contrast to the homogeneous matrix system, the release from such system is
proportional to drug loading. On the basis of dose and solubility hydrophobic matrix
tablet suitable for:-

- High solubility, high dose
- High solubility, medium dose
- High solubility, low dose
- Medium solubility, low dose

Table 1.5: Matrix Diffusion Products.

<table>
<thead>
<tr>
<th>Products</th>
<th>Active ingredient</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fero-Gradumet</td>
<td>Ferrous sulphate</td>
<td>Abbott</td>
</tr>
<tr>
<td>Procan SR tablets</td>
<td>Procainamide HCl</td>
<td>Parke-Davis</td>
</tr>
<tr>
<td>Choledyl SA tablets</td>
<td>Oxtriphylline</td>
<td>Parke-Davis</td>
</tr>
</tbody>
</table>

1.5.3.2 Release of drug from eroding polymer matrix

Polymer chain dissolution from the matrix involves two distinguishable processes.

The first step involves disentanglement of the individual molecules matrix surface,
which depend on rate of hydration. This occurs at a critical polymer concentration,
defined as polymer disentanglement concentration. This polymer concentration
depends on properties of the polymer and solvent.

The second step involves the transport of these molecules from the surface across an
aqueous diffusion layer, adjacent to the matrix, to the bulk solution.
Figure 1.9: A system showing polymer erosion, initial polymer entanglement in the matrix (a), reptating chain disentangling from the system (b) and finally disentangling from the system (c).

a.                           b.                                    c.

Here the disentanglement of the “bold” chain is considered. A test chain is an entangled system of chains is shown in figure 4. When solvent penetrates into the system, the mobility of the test chain increases, and the chain begins to exhibit “reptation”. It has been shown by Gennes, 1971, that the snake like motion of a polymer chain (termed reptation) dominates transport in an entangled system. Reptation causes the test chain to disentangle from the system (Figure b). Then the test chain completely disentangles from the original system as shown in figure c.

1.5.3.3 Advantages of Matrix System

1. Unlike reservoir and osmotic systems, products based on matrix design can be manufactured using conventional processes and equipment.
2. Development cost and times associated with the matrix system generally are viewed as variables, and no additional capital investment is required.
3. A matrix system is capable of accommodating both low and high drug loading and active ingredients with a wide range of physical and chemical properties.
4. Release kinetics and profile can be tailored with modification.
5. Multi-units possible.
6. Very easy to fabricate in a wide range of sizes and shapes.
7. Suitable for both non-degradable and degradable systems.
8. Accidental leakage of total drug component is less likely to occur (30).
1.5.3.4 Disadvantages of the Matrix Systems

Matrix systems lack flexibility in adjusting to constantly changing dosage levels as required by clinical study outcome. When new dosage strength is deemed necessary, more often than not a new formulation and thus additional resources systems lack flexibility in adjusting to constantly changing dosage levels as required by clinical study outcome. When new dosage strength is deemed necessary, more often than not a new formulation and thus additional resources are expected. Furthermore, for some products that require unique release profiles (dual release or delayed plus extended release), more complex matrix-based technologies such as layered tablets are required.

1.6 NSAIDs

Many people use medications to control pain associated with inflammation. Although steroids are effective for reducing inflammation, they can cause many adverse side effects. As an alternative, patients may choose to use drugs in a class known as non-steroidal anti-inflammatory drugs, or NSAIDs, to treat minor pain and inflammation. Diclofenac sodium is one of the more popular NSAIDs. Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed categories of drugs worldwide in the treatment of pain and inflammation in many conditions. NSAIDs are used primarily to treat inflammation, mild to moderate pain, and fever. Specific uses include the treatment of headaches, arthritis, sports injuries, and menstrual cramps.

1.6.1 Mechanism of action

Prostaglandins are a family of chemicals that are produced by the cells of the body and have several important functions. They promote inflammation, pain, and fever; support the blood clotting function of platelets; and protect the lining of the stomach from the damaging effects of acid. Prostaglandins are produced within the body's cells by the enzyme cyclooxygenase (COX). There are two COX enzymes, COX-1 and COX-2. Both enzymes produce prostaglandins that promote inflammation, pain, and fever. However, only COX-1 produces prostaglandins that support platelets and protect the stomach. Nonsteroidal anti-inflammatory drugs (NSAIDs) block the COX enzymes and reduce prostaglandins throughout the body. As a consequence, ongoing
inflammation, pain, and fever are reduced. Since the prostaglandins that protect the stomach and support platelets and blood clotting also are reduced, NSAIDs can cause ulcers in the stomach and promote bleeding.

All non-steroidal anti-inflammatory drugs including diclofenac sodium work by inhibiting cyclooxygenase, the enzymes responsible for synthesizing prostaglandins and compounds that cause inflammation, pain and fever. Although available without a prescription, the use of NSAIDs can cause unwanted adverse effects. However, when used appropriately, NSAIDs are an appropriate treatment option for minor inflammation and pain, especially in musculoskeletal injuries, the Cleveland Clinic says.

### 1.6.2 NSAIDs are used in following conditions:

NSAIDs are used primarily to treat inflammation, mild to moderate pain, and fever. Specific uses include the treatment of headaches, arthritis, sports injuries, and menstrual cramps. Ketorolac (Toradol) is only used for short-term treatment of moderately severe acute pain that otherwise would be treated with opioids. Aspirin (also an NSAID) is used to inhibit the clotting of blood and prevent strokes and heart attacks in individuals at high risk. NSAIDs also are included in many cold and allergy preparations.

### 1.6.3 Differences between NSAIDs

NSAIDs vary in their potency, duration of action, how they are eliminated from the body, how strongly they inhibit COX-1 and their tendency to cause ulcers and promote bleeding. The more an NSAID blocks COX-1, the greater is its tendency to cause ulcers and promote bleeding. One NSAID, celecoxib (Celebrex), blocks COX-2 but has little effect on COX-1, and is therefore further classified as a selective COX-2 inhibitor. Selective COX-2 inhibitors cause less bleeding and fewer ulcers than other NSAIDs.

Aspirin is a unique NSAID, not only because of its many uses, but because it is the only NSAID that inhibits the clotting of blood for a prolonged period (4 to 7 days). This prolonged effect of aspirin makes it an ideal drug for preventing blood clots that cause heart attacks and strokes.
Most NSAIDs inhibit the clotting of blood for only a few hours. Ketorolac (Toradol) is a very potent NSAID and is used for moderately severe acute pain that usually requires narcotics. Ketorolac causes ulcers more frequently than other NSAID. Therefore, it is not used for more than five days. Although NSAIDs have a similar mechanism of action, individuals who do not respond to one NSAID may respond to another.

**1.6.4 Diclofenac Sodium Non-Selective NSAIDs**

As a non-selective NSAID, diclofenac sodium can inhibit cyclooxygenase in many different areas of the body. However, this includes the stomach and intestines, where NSAIDs can cause problems with gastric ulcers and intestinal bleeding. Diclofenac sodium is used for conditions related to inflammation, swelling, stiffness, pain: for relief of signs and symptoms of osteoarthritis; For relief of signs and symptoms of rheumatoid arthritis; for acute or long-term use in the relief of signs and symptoms of ankylosing spondylitis.