INTRODUCTION:

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration belief by oral administration of the drug is well absorbed.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamic as formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

RATIONALE OF SUSTAINED AND CONTROLLED DRUG DELIVERY

The basic rational for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamic of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and pharmacological parameters inherent in the selected route of administration. It is desirable that the duration of drug action becomes more a desiring property of a rate controlled dosage form and less or not at all a property of the drug molecules inherent kinetics properties. Thus optional design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamic of the drugs.

SUSTAINED DRUG DELIVERY SYSTEM

Over the past 30 years, as the expense and complication involved in marketing new entities have increased with concomitant recognition of the therapeutics advantages of
controlled drug delivery, greater attention has been focused on development of sustained or controlled drug delivery system.

Sustained release technology is relatively new field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. With many drugs, the basic goal is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. The design of proper dosage form is an important element to accomplish this goal. Sustained release, sustained action prolonged action, controlled release, extended action, timed release and depot dosage form are term used to identify drug delivery system that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. In the case of oral sustained released dosage form, an effect is for several hours depending upon residence time of formulation in the GIT.

Physician can achieve several desirable therapeutics advantages by prescribing sustained release dosage form. Since, the frequency of drug administration is reduced. Patient compliances can be improved and the drug administration can be made more conventional dosage form is reduced, because more even blood level is maintained in the design of sustained release dosage form. The total amount of drug administered, thus maximum availability with a minimum dose. In addition, the safety margin of high potency drug can be increased and the incidence of both local and systemic adverse effects can be release dosage form gives increased reliability.

Not all the drugs are the suitable candidates for the sustained release dosage form. Ideal characteristic of the drug for the sustained release dosage form are;
• Drug should have a shorter half-life as drug with a longer half-life are inherently long acting drug.

• Drug should be absorbed from large portion of gastrointestinal tract, since absorption must occur through the gut.

• Drug should be having a good solubility profile to be a good candidate for sustained release dosage form.

• Dose of the drug should not be too large, as a larger dose is to be incorporated into sustained release dosage form.

POTENTIAL ADVANTAGES OF SUSTAINED RELEASE DOSAGE FORM

• Avoid patient’s compliance problem due to reduced frequency of dosing.

• Blood level oscillation characteristics of multiple dosing of conventional dosage form are reduced because a more even blood level is maintained.

• Employ a less total drug.
  ➢ Minimize or eliminate local or systemic side effects.
  ➢ Minimize drug accumulation with chronic dosing.
  ➢ Obtained less potential of reduction in drug activity with chronic use.

• Improved efficiency in treatment.
  ➢ Cure or control condition more promptly.
  ➢ Improved control of condition i.e. reduced fluctuation in drug level.
  ➢ Improved bioavailability of some drugs.

• Make a use of special effects, e.g. sustained release aspect for relief of arthritis by dosing before bedtime.

• Economy.
Overall, administrations of sustained release form enable increase reliability of therapy.

MODIFIED RELEASE SYSTEM

To overcome the potential problem associated with conventional drug therapy, modified release systems were developed and may be divided into four categories,

1. Delayed release
2. Sustained release.
   a. Controlled release.
   b. Prolonged release.
3. Site specific release.
4. Receptor release,

1. Delayed release system

Delayed release systems are those that use, repetitive intermittent dosage form.

2. Sustained release system

Sustained release systems are those, which achieves slow release of drug over an extended period of time and in this drug is initially made available to the body in amount to cause the desired pharmacological response.

a) Controlled release system

An ideal controlled drug delivery is that which delivers the drug at predetermined rate, locally or systemically for the predetermined period of time.

b) Prolonged release system

Prolonged release system, prolongs the duration of action without maintaining a constant drug blood level. Thus maintaining constant drug leveling in blood or target tissue.
3. Site specific and receptor release system

Site specific and receptor release and targeted release system refers to targeting of the drug directly to a certain biological location.

![Figure 1: Drug blood level Vs time profile showing relationship between controlled release, Sustained release, and conventional release drug delivery.](image)

Thus now a day controlled release drug delivery systems are most popular in the market over conventional dosage forms.

**RECENT TRENDS IN SUSTAINED DRUG DELIVERY SYSTEM:**

Sustained release dosage forms are categorized as:

- Single unit dosage form.
- Multiple unit dosage form.
- Mucoadhesive system.

**Single unit dosage form**

These refer to diffusion system where the drug is uniformly distributed (dispersed/dissolved) throughout the solid matrix and the release of the drug is
controlled or sustained either by incorporating hydrophilic or hydrophobic filler within the matrix or by coating the drug matrix with a Swellable or non-Swellable polymer film.

These systems can be classified as:

1. **Monolithic system**

If the release rate is controlled or sustained by incorporating hydrophilic or hydrophobic filler within the matrix then the system is called as Monolithic device where the diffusion of drug through the matrix is rate-limiting step.

These are categorized as:

**A. Hydrophobic/Swellable tablet**

Tablet prepared by mixing the drug with hydrophobic/hydrophilic filler appear to extend the release time of the drug from device within the GI tract after oral administration.

**B. Floating tablet or capsule**

Designing of Floating tablet or capsule are called hydro dynamically balanced drug delivery system is based on the principle that device with gravity lesser than that of the gastric juice of stomach and retain the drug in the proximal region of the GIT.

**C. Semisolid matrix system**

In this system, the hydrophobic carrier occurs in an oily semisolid state where the drug is incorporated and the final mass is usually filled into gelatin capsule to prepare the dosage form.

2. **Coated tablet and Similar Multilayer system**

Multilayer systems are designed in such a way that the drug has to cross a barrier or membrane on its way from the device to the physiological environment. The nature and the number of barriers control the release process.
In the simplest form coated tabled comprised a core containing the drug and a coating layer, which surrounds the core. The core is usually the drug either alone or loaded on to an inert material (hydrophilic or hydrophobic).

Multilayered tablet having two or more distinct layers usually prepared by dry coating technique have also been used to formulate sustained or controlled preparations for water- soluble drug. In this case, coating which controls the release process covers the core tablet containing the drug only partially.

3. Osmotic device

In osmotic device usually an osmotic agent (often with an osmotic adjuvant) is contained within a rigid compartment that is separated from the osmotic compartment by a partition. In the physiological environment the aqueous fluid penetrates across the membrane and the increased volume within the osmotic compartment pushes the drug out of the device through a delivery orifice.

MULTIPLE UNIT DOSAGE FORMS

It represents a combination of subnets of the dosage forms, the source of which may either be homogeneous or heterogeneous. It offers the advantages of releasing one of the drug or part of the same drug immediately while remaining drug or parts of the same can be sustained release. These are useful where drug - excipients and drug-drug interactions are inevitable in a single unit dosage form. The various forms are as:

1) Micro granules/Spheroids

2) Beads.

3) Pellets.

4) Microcapsules.

Mucoadhesive systems
It utilizes principle of bioadhesion for optimum delivery of the drug from the device. Bioadhesion is definable as the occurrence in which one biological substance is adhered to another substance, which may either, be of biological or one-biological origin. If the substance is mucosal membrane the phenomenon is known as mucoadhesion. Conventional controlled release dosage forms described above are restrained localized in selected regions of GIT. Mucoadhesive systems are suitable to increase the contact time of drug with absorbing membrane and localization of delivery of drug at target sites.

**MATRIX SYSTEM**

The matrix system is most often used for a drug-controlled release from a pharmaceutical dosage form. Among the innumerable method used in controlled release drug from pharmaceutical dosage form, the matrix system is the most frequently applied; it is release system for delay and control of the release of the drug that is dissolved or dispersed in a resistant supports to disintegration. To define matrix, it is necessary to know the characters that differentiate it from other controlled release dosage forms. Hence the following must be considered:

- The chemical nature of support (generally, the support are formed by polymeric net)
- The physical state of drug (dispersed under molecular or particulate form or both).
- The matrix shape and alteration in volume as a function of time.
- The route of administration. (oral administration remains the most widely used but other route are adaptable)
- The release kinetic model.

The classification of matrix system:
1) **Mineral matrix**
   - Drug retained in the support.
   - Drug absorbed on the support.

2) **Lipidic matrix**
   - Delivery by diffusion.
   - Delivery by surface erosion.

3) **Hydrophilic matrix**
   - Unlimited swelling, delivery by diffusion.
   - Limited swelling controlled delivery through swelling.

4) **Inert matrix**
   - Controlled delivery by diffusion.

5) **Biodegradable matrix**
   - Non-Lipidic.

**ADVANTAGES OF MATRIX SYSTEM**

The interest awakened by matrix system in last few years is completely justified in view of the major advantages. Among these, the following stand out.

- With proper control of manufacturing process, reproducible release profiles are possible.
- There is no risk of “dumping” of a large part of dose, through the structure makes the immediate release of a small amount of active principle unavoidable.
- Their capacity to incorporate active principle is large, which suits them to delivery of large dosage.

**PRINCIPAL OF MODIFIED DRUG RELEASE**

Following either of the two principles can modify drug release:
Barrier principal:

In this method the retardant material is imposed between the drug and elusion medium. Drug release is by diffusion of the drug through the barrier or erosion of the barrier or permeation of the barrier by moisture.

Figure 2: Barrier mediated models of sustained release dosage form regimen

Embedded matrix

In this drug is dispersed embedded in a matrix of retardant material that may be
encapsulated in a particulate form or compressed into the tablet. Drug release occurs by permeation of water leaching extraction of diffusion of drug from the matrix and erosion of matrix material.

**Figure 3: Embedded matrix concept as a mechanism of controlled released in sustained release dosage form design network model a: drug is insoluble in the retardant material, b: Drug is soluble in the retardant material, c: Diffusion profile etc.**

Characterize drug release from matrix system.

**SWELLABLE MATRICES AS SYSTEM FOR ORAL DELIVERY**

Monolithic devices or matrices represent a substantial part of drug delivery systems. Matrices containing swellable polymers are referred to as

- Hydrogel matrices
- Swellable control release systems.
- Hydrophilic matrix tablet

Swellable matrices for oral administration are commonly manufactured as tablet by compression of hydrophilic micro particulate polymers. Therefore, the most appropriate classification for these systems is swellable matrix tablets. They are constituted of a blend of drug and one or more hydrophilic polymers. The release of drug from swellable matrix tablets is based on glassy-rubbery transition of polymer as a result of water penetration into the matrix. The interaction between water, polymer and drug are the primary factors for drug release. However, various formulation variables such as polymer grades, drug-polymer ratio, drug solubility and drug and polymer particle size, can influence drug release rate to greater or lesser degree. The central element of the mechanism of drug release in the gel layer (rubbery polymer), which is formed around
the matrix. The gel layer is capable of preventing matrix disintegration and further rapid water penetration.

Water penetration, polymer swelling drug dissolution and diffusion and matrix erosion are phenomenon determining gel layer thickness. Finally drug release is controlled by drug diffusion through the gel layer and/or by erosion of the gel layer.

**MACHANISM OF DRUG RELEASE FROM MATRIX DEVICES**

I. Dissolution controlled release

Sustained release oral products employing dissolution as the time limiting step are simplest to prepare. If a drug has a rapid rate of dissolution it is possible to incorporate it into a tablet with a carrier that has a slow rate of dissolution. In the dissolution process if the dissolution process is diffusion layer control, the rate of diffusion of drug from the solid surface to the bulk solution through an unstirred liquid film, is the rate limiting step. In this case the dissolution process at steady state would be described by Noyes-Whitney equation

\[ \frac{dc}{dt} = KD (Cs-C) \]  \hspace{1cm} (1)

Where,

\[ \frac{dc}{dt} \] is dissolution rate.

KD dissolution rate constant.

Cs is saturation solubility of drug.

C is the concentration of drug in bulk of the solution.

In relation to diffusion expression, that

\[ KD = D/v \times l \]  \hspace{1cm} (2)

Where,
D is dissolution coefficient

V volume of dissolution media

I is the thickness of unstirred liquid film.

From the above expression it can be seen that rate of dissolution i.e. availability is approximately proportional to the solubility of the drug in the dissolution media i.e. \( C_s \) provided a constant area and diffusion path length are maintained. This equation predicts constant dissolution rate as long as enough drug is present to maintain \( C_s \) constant, provided surface area does not change.

**Dissolution control formulations are categorized as**

a. Encapsulation dissolution control

b. Matrix dissolution control

**a. Encapsulation dissolution control**

This method involves coating individual particles or granules of drug with slowly dissolving material. The coated particles can be compressed directly into tablet as in space tabs or placed in capsule as in spansule products

**b. Matrix dissolution control**

This method involves compression of the drug with a slowly dissolving carrier in a tablet form. Here the rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. This in turn, can be controlled by porosity of the tablet matrix, the presence of hydrophilic and the wettability of the tablet and particles surface.

**II. Diffusion controlled release**

These systems are of two types.

1. **Encapsulated diffusion control**
In this system water-insoluble polymeric material encases a core of drug. Drug will partition into the polymer membrane and exchange with the fluid surrounding the particle or tablet.

The rate drug release is given by the equation.

\[
\frac{dm}{dt} = Adk \Delta c
\]

Where,

- \( A \) is area
- \( D \) is diffusion coefficient
- \( K \) is the partition coefficient of the drug between the membrane and the drug core
- \( l \) is the diffusional path length
- \( \Delta C \) is the concentration difference across the membrane.

An important parameter in the above Eq (3) is the partition coefficient, which is defined as the concentration of the drug in the membrane over the concentration of the drug in core.

2. Matrix diffusion control

In this system, a solid drug is dispersed in lipophilic or a hydrophilic polymer matrix and the rate of release of drug depends on the rate of drug diffusion and not on the rate of solid dissolution.

MATERIAL USED AS RETARDANTS IN MATRIX TABLET

FORMULATION:

These classes of retardant materials are used to prepare matrix tablet formulations.

1. Water insoluble inert materials

- e.g. polyethylene, polyvinyl chloride, methyl acrylate, methacrylate copolymer, ethyl cellulose.
2. Insoluble, erodable materials

e.g. Stearyl alcohol, stearic acid, polyethylene Glycol, carnauba wax, caster wax, polyethylene glycol monosterate, triglycerides.

3. Hydrophillic materials

e.g. Hydroxy propyl methylcellulose, sodium CMC, methylcellulose, hydroxy ethyl cellulose.

Natural gums: Galactomannose (guar gum), chitosan, gum acacia, locust bean gum, sodium alginate, karaya gum, pectin’s, Xanthan gum.

4. Natural polymers

Isabghula husk, tamarind seed polymer.

ADVANTAGES OF HYDROPHILIC MATRIX TABLETS

1. With proper control of the manufacturing process, reproducible release profiles are possible. The variability associated with them is slightly less than that characterizing coated release form.

2. Structure allows an immediate release of small amount of active principle there is no risk of dose dumping.

3. Their capacity to incorporate active principle is large, which suits them to delivery of large doses.

4. The manufacturing processes are notably simple. Tablet formulation can be done via direct compression or by wet granulation techniques.

5. Large variety of nonexpensive gelling agents is approved for oral use by the competent official organization.

6. The safety margin of high- potency drugs can be increased.
7. The drug release from hydrophilic matrices show a typical time dependent profile i.e. decreased drug release with time because of increased diffusion path length.

**FACTORS INFLUENCING THE DRUG RELEASE FROM MATRIX**

I. Choice of matrix material.
II. Amount of drug incorporated in the matrix.
III. Viscosity of the hydrophilic material in aqueous system at a fixed concentration.
IV. Drug: matrix ratio
V. Tablet hardness, porosity, and density variation.
VI. Entrapped air in tablets.
VII. Tablet shape and size.
VIII. Drug particle size.
IX. Solubility of drug in aqueous phase
X. Surfactants and other additives