CHAPTER 1
INTRODUCTION

1.1 Objective of the present work

The title of the thesis is FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF ACECLOFENAC AND ITS PHARMACOKINETIC AND PHARMACODYNAMIC STUDIES IN ANIMAL MODEL. Aceclofenac is a synthetic non-steroidal anti-inflammatory drug (NSAID) used in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It is a newer derivative of diclofenac and has less gastrointestinal complications. It is reported to have plasma half life ($t_{1/2}$) of 4 to 4.3 hours, time of peak plasma concentration ($T_{\text{max}}$) of about 1.25 to 3 hours and the volume of distribution ($V_d$) is approximately 30 litres after an oral dose of conventional tablets of aceclofenac. The drug penetrates into the synovial fluid where the concentration reaches to approximately 60% of that in plasma. It is reported to have considerable first pass metabolism. The successful treatment of arthritis depends on the maintenance of effective drug concentration level in the body for which a constant and uniform bioavailability of the drug from gastrointestinal tract is desired. Sustained release dosage forms deliver the drug at a slow release rate over an extended period of time and achieve this objective

Aceclofenac is usually administered as conventional tablet, containing 100 mg, two times daily. To reduce the frequency of administration and to improve patient compliance, the sustained release formulation of aceclofenac is desirable. Aceclofenac has shorter biological half-life ranging from 4 to 4.3 hours. Since, aceclofenac requires frequent dosing to maintain therapeutic drug concentration, it was chosen as a candidate
for sustained release dosage formulation. For sustained release systems\(^2\), the oral route of drug administration has by far, received the most attention as it is natural, uncomplicated, convenient and safer route. Matrix tablets composed of drug and release retarding material (eg. polymer) offer the simplest approach in designing a sustained release system. Matrix tablets are prepared by either wet granulation or direct compression method. Currently available sustained release matrix tablets are generally prepared by wet granulation method. This study is undertaken to design and evaluate the sustained release tablets of aceclofenac with polymers like hydroxypropyl methylcellulose and ethyl cellulose\(^3\,4\). Among the polymers, hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and hydrophobic polymer such as ethyl cellulose (EC) are frequently used because of their non-toxic nature, easy compression, desirable swelling properties and accommodation to high levels of drug loading. Additionally, these polymers are pH independent materials. In this study, aceclofenac sustained release tablets were prepared by using HPMC K100 M and EC as matrix material. They were evaluated with various parameters like weight variation, hardness, thickness, friability, drug content, in vitro dissolution study, release kinetics, stability study, anti-inflammatory activity, analgesic activity, pharmacokinetic study in rats and sub acute toxicity study.
1.2 Sustained and controlled release drug delivery systems:

Over the past 40 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. The attractiveness of these dosage forms is due to awareness to toxicity and other properties of drug when administered or applied by conventional method in the form of tablets, capsules, injectables, ointments, etc. Usually conventional dosage forms produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. These factors as well as factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So controlled release dosage form is a dosage form that releases one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

1.3 Terminology:

Modified release delivery systems may be divided conveniently in to four categories,
A. Delayed release

B. Sustained release

   (i) Controlled release

   (ii) Extended release

C. Site specific targeting

D. Receptor targeting

A. Delayed release:

A delayed release dosage form is designed to release the drug at a time other than promptly after administration. The delay may be time based or based on the influence of environmental conditions, like gastrointestinal pH.

B. Sustained release:

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

(i) Controlled release:

These systems also provide a slow release of drug over an extended period of time and also can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the systems is successful at maintaining constant drug levels in the target tissue or cells.
(ii) **Extended release:**

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

**C. Site specific targeting:**

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is adjacent to or in the diseased organ or tissue.

**D. Receptor targeting:**

These systems refer to targeting of a drug directly to a certain biological location. In this case the target is the particular receptor for a drug within an organ or tissue. Site specific targeting and receptor targeting systems specify the spatial aspect of drug delivery and are also considered to be controlled drug delivery systems.

**1.4 Release rate and dose consideration:**

As already mentioned, conventional dosage forms include solutions, capsules, tablets and emulsions etc. These dosage forms can be considered to release their active ingredients into an absorption pool immediately.

\[ k_r \quad k_a \quad k_c \]

\[
\text{Dosage form} \rightarrow \text{Absorption pool} \rightarrow \text{Target area} \rightarrow \text{Elimination}
\]

\[
\text{Drug release} \rightarrow \text{Absorption}
\]
The absorption pool represents a solution of the drug at the site of absorption where

\[ k_r \] – First order rate constant for drug release

\[ k_a \] – First order rate constant for drug absorption

\[ k_c \] - First order rate constant for overall drug elimination

For immediate release dosage forms, \( k_r \ll k_a \) or alternatively absorption of drug across a biological membrane is the rate limiting step in the delivery of drug to its target area.

For non-immediate release dosage forms, \( K_r \ll K_a \), that is, release of drug from the dosage form is the rate limiting step. This causes the above kinetics scheme to reduce to

\[
\begin{align*}
\text{Dosage form} & \quad \rightarrow \quad \text{Target area} \quad \rightarrow \quad \text{Elimination} \\
\text{Drug release} & \\
\end{align*}
\]

Thus, the effort to develop a delivery system that releases drug slowly must be directed primarily at altering the release rate by affecting the value of \( k_r \).

The ideal goal in designing a controlled-release system is to deliver drug to the desired site at a rate according to the needs of the body. The diagram for
A hypothetical drug blood level versus time curve for a conventional solid dosage form and a controlled release product is shown below:

![Graph showing hypothetical drug blood level versus time curves](image)

The objective in designing a sustained release system is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level. This constant rate should be analogous to that achieved by continuous intravenous infusion where a drug is provided to the patient at constant rates just equal to its rate of elimination. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time, i.e., release from the dosage form should follow zero-order kinetics, as shown by:

\[
k_r^0 = \text{Rate in} = \text{Rate out} = k_e \cdot C_d \cdot V_d
\]

where

\[
k_r^0 = \text{Zero order rate constant for drug release (amount / time )}
\]
\[
k_e = \text{First order rate constant for overall drug elimination (time^{-1})}
\]
\[ C_d = \text{Desired drug level in the body (amount / volume)} \]

\[ V_d = \text{Volume space in which drug is distributed} \]

For many drugs, more complex elimination kinetics and other factors affect their deposition. This affects the nature of release kinetics necessary to maintain a constant drug blood level. It is important to recognize that while zero – order release may be desirable theoretically, non zero – order release may be equivalent clinically to constant release in many cases.

Aside from the extent of intra and inter subject variation is the observation that for many drugs, modest changes in drug tissue levels do not result in an improvement in clinical performance. Thus, a constant drug level may be indistinguishable clinically from an inconsistent drug level.

To achieve a therapeutic level promptly and sustain the level for a given period of time, the dosage form generally consists of two parts: an initial primary dose, \( D_i \), which release drug immediately and a maintenance or sustaining dose, \( D_m \).

The total dose, \( W \), thus required for the system is:

\[ W = D_i + D_m \]

For a system in which the maintenance dose releases the drug by a zero order process for a specified period of time, the total dose is:
\[ W = D_i + k_r^0 + T_d \]

where

\[ k_r^0 = \text{Zero order rate constant for drug release} \]
\[ T_d = \text{Total time desired for a sustained release from one dose} \]

If the maintenance dose begins release of drug at the time of dosing (\( t = 0 \)); it will add to that which is provided by the initial dose, thus increasing the initial drug level. In this case a correction factor is needed to account for the added drug from the maintenance dose.

\[ W = D_i + k_r^0 \cdot T_d - k_r^0 \cdot T_p \]

The correction factor, \( k_r^0 \cdot T_p \) is the amount of drug provided during the period from \( t=0 \) to the time of the peak drug level, \( T_p \). No correction factor is needed if the dosage form is constructed in such a fashion that the maintenance dose does not begin to release drug until time \( T_p \). Satisfactory approximation of a constant drug level can be obtained by suitable combinations of the initial dose and a maintenance dose that releases its drug by a first order process. The total dose for such a system is:

\[ W = D_i + \left( \frac{k_e C_d}{k_r} \right) V_d \]

where \( k_r = \text{First order drug release constant (time}^{-1}) \)

If the maintenance dose begins releasing drug at \( t=0 \), a correction factor is required just as it was in the zero order case. The correct expression in this case is:
\[ W = D_t + (k_e C_d / k_r) V_d - D_m k_r T_p \]

To maintain drug blood levels within the therapeutic range over the entire time course of therapy, most controlled – release drug delivery systems are, like conventional dosage forms, administered as multiple rather than single doses. For an ideal controlled – release system that releases drug by zero order kinetics, the multiple dosing regimen is analogous to that used for a constant intravenous injection. For those controlled release systems having release kinetics other than zero order, the multiple dosing regimen is more complex.

1.5 Potential advantages of controlled drug therapy⁵:

All the controlled release products share a common goal of improving drug therapy over that achieved with their non – controlled counterparts. This improvement in drug therapy lead to the following several potential advantages:

A. Avoids patient compliance problems

B. Reduces the total dose administered leading to

(i) Minimisation or elimination of local side effects

(ii) Minimisation or elimination of systemic side effects

(iii) Less potentiation or reduction in drug activity with chronic use

(iv) Minimisation of drug accumulation with chronic dosing

C. Improves efficiency in treatment leading to

a. Cure or control of condition more promptly
b. Improvement in control of condition (i.e.) reduction in fluctuation in drug level

c. Improvement of bio availability of some drugs

d. Special effects such as sustained release aspirin for morning relief of arthritis by dosing before bed time.

D. Economy.

1.6 Oral sustained and controlled release systems:

Totally three types of oral controlled release systems are available-classified based on the release mechanism:

1.6.1 – Dissolution controlled release system

1.6.2 – Diffusion controlled release system

1.6.3 – Bio erodible and combination diffusion and dissolution systems

1.6.1 – Dissolution controlled release system:

Here the rate – limiting step is dissolution. This being the case, sustained release preparation of drugs can be made by decreasing the rate of dissolution. This approach is achieved by preparing appropriate salts or derivatives, coating the drug with a slow dissolution material or incorporating it into a tablet with a slowly dissolving carrier.

Dissolution controlled systems can be made either by rate controlling coats or by administering the drug as a group of beads that have coating of different thickness. In the first case if the outer layer is a quickly releasing bolus of drug, initial levels of drug in the body can be quickly established with pulsed intervals. In the second
case since the beads have different coating thickness, their release will occur in a progressive manner.

Those with the thinnest layer will provide the initial dose and the maintenance of drug levels at later periods will be achieved from those with thicker coating. This dissolution process at steady state is described by the Noyes-Whitney equation:

\[
d\frac{C}{dt} = k_d A \left( C_s - C \right) = \frac{D}{h} A \left( C_s - C \right)
\]

where

- \(dC/dt\) – dissolution rate
- \(k_d\) – dissolution rate constant
- \(D\) – diffusion co-efficient
- \(C_s\) – saturation solubility of the solid
- \(C\) – concentration of solute in the bulk solution

The above equation predicts that the rate of release can be constant only if the following parameters are constant:

a) Surface area
b) Diffusion co-efficient
c) Diffusion layer thickness
d) Concentration difference
But these parameters are not easily maintained constant, especially surface area. It can be related to the weight of the particle, which is under the assumption of sink conditions. The above equation can be rewritten as the cube root dissolution equation

\[ W_0^{1/3} - W^{1/3} = K_D t \]

where

\[ K_D = \text{cube root dissolution rate constant} \]

\[ W_0 = \text{initial weight} \]

\[ W = \text{weight of the amount remaining in time } t. \]

**1.6.2 – Diffusion system:**

In this system release rate of a drug is dependent on its diffusion through an inert membrane barrier. Usually, this barrier is an insoluble polymer.

It may be,

a) Reservoir devices

b) Matrix devices

a) Reservoir devices:

Reservoir devices are characterized by a core of drug, the reservoir surrounded by a polymeric membrane. The nature of the membrane determines the rate of release of drug from the system.
The process of diffusion is described by Fick’s equation. This equation states that the amount of drug passing across a unit area is proportional to the concentration difference across that plane.

\[ J = -D \frac{dC_m}{dx} \quad (1) \]

where

\( J \) = given in units of amount/area – time,

\( D \) = is the diffusion co-efficient of the drug in the membrane (Area / time).

\( \frac{dC_m}{dx} \) = represents the rate of change in concentration of drug in the membrane over a distance \( x \).

Equation (1) can be integrated and simplified to give,

\[ J = DK \Delta C/d \quad (2) \]

where

\( K \) = partition co efficient

\( \Delta C \) = concentration differences across the membrane

\( d \) = thickness of the diffusion layer

In the equation (2) it is assumed that ‘D’ and ‘K’ are constant.

Drug release will vary, depending on the geometry of the system. The simplest system to consider is that of a slab, where drug release is from only one surface. In this case equation (2) can be written as:
\[
dM_t/dt = ADK\Delta C/d
\]

where

\( M_t \) = mass of drug released after time ‘t’

\( dM_t/dt \) = steady – state release rate at time ‘t’

\( A \) = surface area of the device

\( D \) and \( K \) are constants

The left side of the equation (3) represents the release rate of the system. A true controlled release system with a zero-order release rate is possible if all of the variables on the right side of equation (3) remain constant. But it is very difficult to maintain all the parameters constant.

In the case of reservoir devices, a system that is used relatively soon after construction will demonstrate a large time in release, since it will take time for the drug to diffuse from the reservoir to the membrane surface. On the other hand, systems that are stored will demonstrate a brush effect since on standing the membrane becomes saturated with available drug. The magnitude of these effects is dependent on the diffusing distance (ie the membrane thickness).

Advantages:

i) These devices can offer zero order release of the drug.
ii) Kinetics of a particular drug can be controlled by changing the characteristics of the polymer to meet the particular therapeutic condition.

Disadvantages:

i) System must be physically removed from implant site

ii) Difficult to deliver high molecular weight compounds

iii) Generally increased cost per dosage unit

iv) Potential toxicity if system fails

b) Matrix devices:

Matrix devices consist of drug dispersed homogenously throughout a polymer matrix. In this model, drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix.

This process occurs at the interface between the bathing solution and the solid drug moving toward the interior. For this system, rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of the dissolved drug leaving the matrix.

Derivation of the mathematical model to describe this system involves the following assumptions:

- A pseudo steady state is maintained during drug release.
- The diameter of drug particles is less than the average distance of drug diffusion through the matrix.
- The bathing solution provides sink conditions at all times.
- The diffusion co-efficient of the drug in the matrix remains constant i.e., no change occurs in the characteristics of the polymer matrix.
- The rate of release of drug dispersed in an inert matrix system, has been derived by Higuchi

\[
nM/dh = C_o dh - C_s/2 \quad \text{(1)}
\]

where

\[
\text{dM} = \text{change in amount of drug released per unit area}
\]
\[
\text{dh} = \text{change in the thickness of the zone of matrix that has been depleted of drug}
\]
\[
C_o = \text{total amount of drug in unit volume of matrix}
\]
\[
C_s = \text{saturated concentration of drug within the matrix}
\]

From diffusion theory,

\[
nM = (D_m C_s/ h) dt \quad \text{(2)}
\]

where

\[
D_m \text{ is the diffusion co-efficient in the matrix equation (1) and (2). Integrating and solving for ‘h’ gives:}
\]
\[
M = (C_s D_m (2 C_o - C_s) t)^{1/2} \quad \text{(3)}
\]

When the amount of drug is in excess of the saturated concentration, that is \(C_o \gg C_s\),

\[
M = (2 C_s D_m C_o t)^{1/2} \quad \text{(4)}
\]

Equation 4 indicates that the amount of drug released is a function of square root of time.

The drug release from a porous or granules matrix can be described by

\[
M = (D_s C_a \{ P/T \} [2 C_o - P C_a] t)^{1/2}
\]

where

- \(P\) = porosity of the matrix
- \(T\) = tortuosity
- \(C_a\) = solubility of the drug in the release medium
- \(D_s\) = diffusion co-efficient in the release medium

The system is slightly different from the previous matrix system in that the drug is able to pass out the matrix through fluid filled channels and does not pass through the polymer directly.

Disadvantage of matrix diffusion system:

1) Can not obtain zero order release.

2) Removal of remaining matrix is necessary for implanted system.
Advantage of matrix diffusion system:

1) Easier to produce than reservoir devices.
2) Can deliver high molecular weight compounds.

1.6.3. Bioerodible and combination diffusion and dissolution system:

Therapeutic systems are dependant not only on dissolution or diffusion system. In practice, however, the dominant mechanism for release will be either dissolution rate limited or diffusion controlled. Bioerodible device constitutes a group of systems for which release characteristics are complex. The mechanism of release from simple erodible slabs, cylinders and spheres can be described by the following mathematical model:

$$\frac{M_t}{M} = 1 - \left( 1 - K_0 \frac{t}{C_0 a} \right)^n$$

where

- $M_t$ = mass of drug release at time $t$
- $M$ = mass release at infinite time
- $a$ = radius of a sphere or cylinder or the half height of a slab
- $n$ = 3 for a sphere, 2 for a cylinder and 1 for a slab

This system is the combination of both diffusion and dissolution of matrix material and drug. Drug not only diffuses out of the dosage form but the matrix itself undergoes a dissolution process.
The complexity of the system arises from the fact that as the polymer dissolves, the diffusional path length for the drug may change. This usually results in a moving boundary diffusion system. Zero order release can occur only if surface erosion occurs and surface area does not change with time.

An advantage of such a system is that the bio erodible property of the matrix does not result in a ghost matrix. The disadvantage of these matrix systems is that release kinetics is often hard to control.

Another method for the preparation of bioerodible system is to attach the drug directly to the polymer by a chemical bond. Generally drug is released from the polymer by hydrolysis or enzymatic reactions.

Advantage of such system is better control of the rate of release. Another advantage of the system is the ability to achieve very high drug loading.

Third type is the swelling controlled matrix. Here the drug is dissolved in the polymer, but instead of an insoluble or eroding polymer, swelling of the polymer occurs. This allows entrance of water, which causes dissolution of the drug and diffusion out of the swollen matrix. In these systems the release rate is highly dependent on the polymer swelling rate, drug solubility and the amount of soluble fraction in the matrix. This system usually minimizes burst effects, since polymer swelling must occur before drug release.

1.7 Drug properties relevant to controlled release formulation:

The design of controlled release delivery systems 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 drug. Each of these variables are interrelated and this imposes certain constraints upon the choices for the route of delivery, the design of the delivery system and the length of therapy. Properties of drug are very important for designing a sustained release dosage form. Mainly physiochemical and biological properties of the drug are more important.

1.7.1 Physiochemical properties:

a) Aqueous solubility and pKa:

A drug to be absorbed it must first dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane. Two of the most important physiochemical properties of a drug that influence its absorptive behaviour are its aqueous solubility pKa. These properties play an influential role in the performance of controlled release systems.

The aqueous solubility of a drug influences its dissolution rate, which in turn establishes its concentration in solution and hence the driving force for diffusion across membrane. Dissolution rate is related to aqueous solubility as shown by the Noyes – Whitney equation, Under sink condition it is:

\[ \frac{dc}{dt} = K_d A C_s \]

where

\[ \frac{dc}{dt} = \text{dissolution rate} \]
\( K_D = \) dissolution rate constant

\( A = \) total surface area of the particle

\( C_s = \) aqueous saturation solubility of the drug

The dissolution rate is constant only if surface area ‘A’ remains constant. But the important point to note is that the initial rate is directly proportional to aqueous solubility, \( C_s \). Therefore, the aqueous solubility of a drug can be used as a first approximation of its dissolution rate. Drugs with low aqueous solubility have low dissolution rates and usually suffer from oral bioavailability problems.

Aqueous solubility of weak acids and bases is governed by the pKa of the compound and pH of the medium.

For a weak acid:

\[
S_t = S_o \left( 1 + \frac{K_a}{[H^+]} \right) = S_o \left( 1 + 10^{pH-pK_a} \right) \quad ------- (1)
\]

where

\( S_t = \) total solubility (both ionized and un-ionized forms) of the weak acid

\( S_o = \) solubility of the un-ionized form

\( K_a = \) acid dissolution constant

\( H^+ = \) hydrogen ion concentration of the medium

Equation (1) predicts that the total solubility, \( S_t \), of a weak acid with a given pKa can be affected by the pH of the medium.
For a weak base:

\[
S_t = S_o ( 1 + [H^+] / K_a ) = S_o ( 1 + 10^{pK_a - \text{pH}} ) \quad (2)
\]

where

- \( S_t \) = total solubility (both conjugate acid and free base forms) of the weak base
- \( S_o \) = solubility of the free base form
- \( K_a \) = acid dissociation constant of the conjugate acid

So, total solubility, \( S_t \), of a weak base whose conjugate acid has a given pKa, can be affected by the pH of the medium.

In general, extreme aqueous solubility of a drug is undesirable for formulation into a controlled release product. A drug with very low solubility and a slow dissolution rate will exhibit dissolution limited absorption and yield an inherently sustained blood level. Formulation of such a drug into a controlled release system may not provide considerable benefits over conventional dosage forms.

Any system relying upon diffusion of drug through a polymer as the rate limiting step in release would be unsuitable for a poorly soluble drug, since the driving force for diffusion is the concentration of drug in the polymer or solution, and this concentration would be low. For a drug with very high solubility and a rapid dissolution rate, it often is quite difficult to decrease its dissolution rate and lower its absorption. Preparing a slight soluble form of a drug with normally high solubility is, however, one possible method for preparing controlled release dosage forms.
b) Partition coefficient:

Between 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 lipid like barriers. A major criteria in the evaluation of the ability of a drug to penetrate these lipid membranes is its apparent oil / water partition coefficient defined as

\[ K = \frac{C_o}{C_w} \]

where

- \( C_o \) = equilibrium concentration of all forms of the drug e.g., ionized and unionized in an organic phase at equilibrium
- \( C_w \) = equilibrium concentration of all forms in the aqueous phase

In general, drugs with extremely large values of ‘K’ are very oil soluble and will partition into membrane quite readily. The relationship between tissue permeation and partition coefficient for the drug generally is defined by the Hansch correlation, which describes a parabolic relationship between the logarithm of the activity of a drug or its ability to be absorbed and the logarithm of its partition coefficient.

The explanation for this relationship is that the activity of a drug is a function of its ability to cross membranes, and interact with the receptor. The more effectively a drug crosses membranes, the greater its activity. There is also an optimum partition coefficient for a drug in which it most effectively permeates membranes and thus shows greatest activity. The value of K at which optimum activity is observed is approximately 1000 / 1. Drug with a partition coefficient that is higher or lower than
optimum, is in general, poorer candidate for formulation into controlled – release dosage forms.

c) Drug stability:

One important factor for oral dosage forms is the loss of drug through acid hydroxyl and / or metabolism in GI tract. Since a drug in the solid state undergoes degradation at a much slower rate than a drug in suspension or solution. It is possible to improve significantly the relative bio availability of a drug that is unsuitable in GI tract by placing it in a slowly available controlled release form. For those drugs that are unstable in the stomach, the most approximate controlling unit would be one that releases its content only in the environment of the intestine. The reverse is the case for those drugs that are unstable in the environment of the intestine, the most appropriate controlling unit in this case would be one that releases its content only in the stomach. So, drugs with significant stability problems in any particular area of the GI tract are less suitable for formulation into controlled release systems that deliver their content uniformly over the length of the GI tract. Controlled drug delivery systems may provide benefits for highly unstable drugs because the drug may be protected from enzymatic degradation by incorporation into a polymeric matrix.

d) Protein binding:

There are some drugs having tendency to bind with plasma proteins ( eg. albumin ) which cause retention of the drug in the vascular space. The main force of attraction responsible for binding is Van der Waals forces, hydrogen bonding and
electrostatic forces. In general, charged compounds have a greater tendency to bind a protein than uncharged compounds, because of electrostatic effects.

If a drug is protein bound, then the distribution of the drug into the extravascular space is governed by the equilibrium process of dissociation of the drug from the protein. The drug protein complex can serve therefore as a reservoir in the vascular space for controlled drug release of extra vascular space for controlled drug release. Thus, the protein binding characteristics of a drug can play a significant role in its duration of 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 drugs and such drugs generally do not require a controlled – release dosage form. However, drugs that exhibit a high degree of binding to plasma protein also might bind to biopolymers in the GI tract, which could have an influence on controlled – drug therapy.

1.7.2 Biological properties :

Absorption:

The rate, extent and uniformity of absorption of a drug are important factors when considering to formulate into a controlled – release system. Since the rate – limiting step in drug delivery from a controlled – release system is its release from a dosage form, rather than absorption, a rapid rate of absorption of drug relative to its release is essential if the system is to be successful. In the case of controlled release dosage forms where $K_r \ll K_a$ this becomes more critical in the case of oral administration. Assuming that the transit time of a drug through the absorption area of the GI tract is between 9 and 12 h, the maximum absorption half life should be 3 to 4 h. This
corresponds to a minimum absorption rate constant $K_a$ of 0.17 to 0.23 $h^{-1}$ necessary for about 80 to 95% absorption over a 9 to 12 h transit time.

For a drug with a very rapid rate of absorption (i.e., $K_a >> 0.23$ $h^{-1}$), the above discussion implies that a first order release constant $K_r < 0.17$ $h^{-1}$ is likely to result in unacceptably poor bio-availability in many patients. Therefore, slowly absorbed drugs will be difficult to formulate into controlled release systems where the criterion that $K_r << K_a$ must be met.

Distribution:

The distribution of drug into vascular and extravascular spaces in the body is an important factor in its overall elimination kinetics. Two parameters that are used to describe the distribution characteristics of a drug are its apparent volume of distribution and the ratio of drug concentration in the tissue to that in plasma at the steady state, the so-called T/P ratio. The magnitude of apparent volume of distribution can be used as a guide for additional studies and as a predictor for a drug – dosing regimen and hence the need to employ a controlled – release system.

Metabolism:

Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bio – availability from slower – releasing dosage forms. Most intestinal wall enzyme systems are saturable. As the drug is released at a slower rate to these regions, less total drug is presented to the enzymatic process during a specific period allowing more complete conversion of drug to its
metabolite. Formulation of these enzymatically susceptible compound as pro drug is another viable solution.

1.7.3 Biological half life:

The usual goal of an oral sustained release product is to maintain therapeutic blood levels over an extended period. To this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half life. Each drug has its own characteristic elimination rate, which is the sum of all elimination processes including metabolism, urinary excretion and all other processes that permanently remove drug from blood stream.

Therapeutic compounds with short half life are excellent candidates for sustained – release preparations, since this can reduce dosage frequency. However, this is limited, in that drugs with very short biological half life as it may require excessively large amounts of drug in each dosage unit to maintain sustained effect, forcing the dosage form itself to become large.

In general, drugs with half life shorter than two h are poor candidates for sustained release preparations. Drugs with long half life, more than 8 h, are also generally not used in sustained forms, since their effect is already sustained.

1.7.4 Side effects and safety consideration:

There are very few drugs whose specific therapeutic concentrations are known. Instead, a therapeutic concentration range is listed, with increasing toxic effects
expected above this range and a fall off in desired therapeutic response observed below the range.

The most widely used measure of the margin of safety of a drug is its therapeutic index (TI).

\[ TI = \frac{TD_{50}}{ED_{50}} \]

where

\( TD_{50} = \) median toxic dose.

\( ED_{50} = \) median effective dose.

For very potent drugs, whose therapeutic concentration is narrow, the value of TI is small. In general, larger the value of TI, the safer the drug. Drug with very small value of TI usually are poor candidates for formulation into controlled release product. A drug is considered to be relatively safe if its TI value exceeds 10.

### 1.7.5 Dose size:

Sustained release system is designed to reduce repetitive dosing of conventional dosage form. For those drugs requiring large conventional doses, the volume of the sustained dose may be so large as to be impractical or unacceptable, depending on the route of administration. The same may be true for drugs that require a large release rate from the controlled release system, eg., drugs with shorter half life. For oral route, the volume of product is limited by patient acceptance.
A list of materials used as retardants in matrix tablet formulations is provided below:

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Matrix characteristics</th>
<th>Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Insoluble, Inert</td>
<td>Poly ethylene, poly vinyl chloride, methyl acrylate, methacrylate co – polymer, ethyl cellulose.</td>
</tr>
<tr>
<td>2.</td>
<td>Insoluble, Erodable</td>
<td>Carnuaba wax, stearyl alcohol, stearic acid, PEG, hydrogenated castor oil, PEG monostearate, triglycerides.</td>
</tr>
<tr>
<td>3.</td>
<td>Hydrophilic</td>
<td>Methyl cellulose, hydroxy methyl cellulose, HPMC, sodium CMC, sodium alginate, carboxy polymers.</td>
</tr>
</tbody>
</table>