Sustained release drug delivery systems are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. There are several advantages of sustained release drug delivery over conventional dosage forms like improved patient compliance due to less frequent drug administration, maximum utilization of the drug, increased safety margin of potent drug, reduction of fluctuation in steady-state drug levels, reduction in healthcare costs through improved therapy and shorter treatment period. Wide varieties of polymers like Hydroxy Propyl Methyl Cellulose (HPMC), Carboxy Methyl Cellulose (CMC), Ethyl Cellulose (EC), Cellulose Acetate Phthalate, HPMC K100M, Xanthan gum, Carrageenan gum, Karaya gum, HPMC K15, Carbopol 971P and Carbopol 974P etc. are available for retarding the release rate of drugs hence sustains the action of drugs. This review article describes the basic information regarding sustained-release formulation, its advantages, disadvantages, selection of drug for sustain release, mechanism of release, different types, and factor involved in oral sustained-release dosage form design.

Keywords: Sustained-release, Conventional dosage form, Dissolution, Diffusion, Matrix.
Figure 1.1: A hypothetical plasma-concentration time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations

Ideally a sustained release oral dosage form is designed to release rapidly some predetermined fraction of the total dose in to GI tract. This fraction (loading dose) is an amount of drug, which will produce the desired pharmacological response as promptly as possible and the remaining fraction of the total dose (maintenance dose) is then release at a constant rate. The rate of the drug absorption from the entire maintenance dose into the body should equal to the rate of the drug removal from the body by all the processes over the time for which the desired intensity of pharmacological response is required.\textsuperscript{2, 3}

Ideally two main objectives exist for these systems: Spatial delivery, which is related to the control over the location of drug release and temporal drug delivery, in which the drug is delivered over an extended period of time during treatment.\textsuperscript{3, 4}

Disadvantages of Conventional Drug Delivery System

1. Inconvenient
2. Difficult to monitor
3. Careful calculation necessary to prevent overdosing
4. Large amounts of drug can be “lost” when they don’t get to the target organ
5. Drug goes to non-target cells and can cause damage
6. Expensive (using more drug than necessary).\textsuperscript{5}

Advantages of sustained release dosage forms

1. Reduction in frequency of intakes.
2. Reduce side effects.
3. Uniform release of drug over time.
4. Better patient compliance.\textsuperscript{5, 6}

Disadvantages of sustained release drug delivery

1. Increased cost.
2. Toxicity due to dose dumping.
4. Risk of side effects or toxicity upon fast release of contained drug (mechanical failure, chewing or masticating, alcohol intake).
5. Increased potential for first-pass clearance.
6. Need for additional patient education and counseling.\textsuperscript{6, 7}

1.2 RATIONALE OF SUSTAINED AND CONTROLLED DRUG DELIVERY

The basic rationale for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and physiological 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 pharmacodynamics of the drugs.

1.2.1 Types of Non-immediate release drug delivery system

The conventional dosage forms are immediate release type. Non-immediate release delivery systems may be divided conveniently into three categories: \textsuperscript{8, 9, 10}

Delayed release drug delivery systems:
Repeat action DDS
Timed release DDS

Sustained release drug delivery systems:
Controlled release DDS
Prolonged release DDS

Site specific and receptor release drug delivery systems:
Organ targeting DDS
Cellular targeting DDS
Sub cellular targeting DDS

1. Delayed Release system

These systems are those systems that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release system include repeat action tablets and capsules, as shown in Figure 1.2. A delayed release dosage form does not produce or maintain uniform drug blood levels within the therapeutic range.

![Diagram of drug levels in the blood with Repeat action drug delivery systems](Figure 1.2)
2. **Sustained Release system**

It includes any drug delivery system that achieves slow release of drug over an extended period of time.

3. **Controlled Release system**

If the system is successful at maintaining constant drug level in the blood or target tissues, it is considered as a controlled release system. Drug delivery systems from which therapeutic agents may be automatically delivered at predefined rates over a long period of time are called as controlled drug delivery systems.

4. **Prolonged Release system**

If without maintaining constant level, the duration of action is extended over that achieved by conventional delivery; it is considered as a prolonged release system. This is illustrated in Figure 1.3.

![Figure 1.3: Drug levels in the blood with prolonged release drug delivery systems](image)

5. **Site-Specific and Receptor Release**

It refers to targeting of a drug directly to a certain biological location. In the case of site-specific release, the target is a certain organ or tissue, while for receptor release; the target is the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspects of drug delivery.

1.2.2 **Principle of sustained release drug delivery**

The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme.

![Scheme](image)

The absorption pool represents a solution of the drug at the site of absorption, and the term $Kr$, $Ka$ and $Ke$ are first order rate-constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that $Kr \gg \gg \gg Ka$. Alternatively speaking the absorption of drug across a biological membrane is the rate-limiting...
The main objective in designing a sustained release delivery system is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. It means that the drug release from the dosage form should follow zero-order kinetics, as shown by the following equation:

\[ K^0_r = \text{Rate In} = \text{Rate Out} = K_e C_d V_d \]  

Where,
- \( K^0_r \): Zero-order rate constant for drug release - Amount/time
- \( K_e \): First-order rate constant for overall drug elimination
- \( C_d \): Desired drug level in the body – Amount/volume, and
- \( V_d \): Volume space in which the drug is distributed

Sustained-release systems include any drug-delivery system that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this being of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered a controlled-release system.

1.2.3 Classification of sustained/controlled release systems
(A) Monolithic Systems (Matrix System)

Monolithic (matrix) devices are possibly the most common of the devices for controlling the release of drugs. This is possibly because they are relatively easy to fabricate, compared to reservoir devices, and there is not the danger of an accidental high dosage that could result from the rupture of the membrane of a reservoir device. In such a device the active agent is present as dispersion within the polymer matrix, and they are typically formed by the compression of a polymer/drug mixture or by dissolution or melting. The dosage release properties of monolithic devices may be dependent upon the solubility of the drug in the polymer matrix or, in the case of porous matrixes, the solubility in the sink solution within the particle's pore network, and also the tortuosity of the network (to a greater extent than the permeability of the film), dependent on whether the drug is dispersed in the polymer or dissolved in the polymer. For low loadings of drug, (0 to 5% w/v) the drug will be released by a solution-diffusion mechanism (in the absence of pores). At higher loadings (5 to 10% w/v), the release mechanism will be complicated by the presence of cavities formed near the surface of the device as the drug is lost: such cavities fill with fluid from the environment increasing the rate of release of the drug.
It is common to add a plasticizer (e.g., poly ethylene glycol), or surfactant, or adjuvant (i.e., an ingredient which increases effectiveness), to matrix devices (and reservoir devices) as a means to enhance the permeability (although, in contrast, plasticizer may be fugitive, and simply serve to aid film formation and, hence, decrease permeability - a property normally more desirable in polymer paint coatings). It was noted by that the leaching of PEG acted to increase the permeability of (ethyl cellulose) films linearly as a function of PEG loading by increasing the porosity; however, the films retained their barrier properties, not permitting the transport of electrolyte.\textsuperscript{13,14}

It was deduced that the enhancement of their permeability was as a result of the effective decrease in thickness caused by the PEG leaching. This was evinced from plots of the cumulative permeant flux per unit area as a function of time and film reciprocal thickness at a PEG loading of 50\% w/w: plots showing a linear relationship between the rate of permeation and reciprocal film thickness, as expected for a (Fickian) solution-diffusion type transport mechanism in a homogeneous membrane. Extrapolation of the linear regions of the graphs to the time axis gave positive intercepts on the time axis: the magnitude of which decreased towards zero with decreasing film thickness. These changing lag times were attributed to the occurrence of two diffusion flows during the early stages of the experiment (the flow of the 'drug' and also the flow of the PEG), and also to the more usual lag time during which the concentration of permeant in the film is building-up. Caffeine, when used as a permeant, showed negative lag times. No explanation of this was forthcoming, but Donbrow noted that caffeine exhibited a low partition coefficient in the system, and that this was also a feature of aniline permeation through polyethylene films which showed a similar negative time lag.\textsuperscript{15}

**Diffusion controlled by Fick’s law**

\[ J = -D \frac{dC_m}{dx} \] \hspace{1cm} (1.2)

Where,
- J = flux of the drug across a membrane in the direction of decreasing concentration,
- D = Diffusion coefficient of the drug, and
- \( dC_m /dx \) = Change in the concentration of the drug in the membrane.

**Figure 1.4: Rate Control: Matrix System\textsuperscript{15}**
(B) Reservoir Systems

A typical approach to controlled release is to encapsulate or contain the drug entirely (e.g., as a core within a polymer film or coat (i.e., microcapsules or spray/pan coated cores). Kala H., et al has reviewed the Film coating (with particular reference to polymers and their additives), whilst Arshady et al., has reviewed microencapsulation\textsuperscript{16,17,18}

When the device contains dissolved active agent, the rate of release decreases exponentially with time as the concentration (activity) of the agent (i.e., the driving force for release) within the device decreases (i.e., first order release). If, however, the active agent is in a saturated suspension, then the driving force for release is kept constant (zero order) until the device is no longer saturated. Alternatively, the release-rate kinetics may be desorption controlled, and a function of the square root of time.\textsuperscript{19}

The research workers investigated the effect of deionised water on salt containing tablets coated in poly (ethylene glycol) (PEG)-containing silicone elastomer, and also the effects of water on free films. The release of salt from the tablets was found to be a mixture of diffusion through water filled pores, formed by hydration of the coating, and osmotic pumping. KCl transport through films containing just 10% PEG was negligible, despite extensive swelling observed in similar free films, indicating that porosity was necessary for the release of the KCl which then occurred by 'trans-pore diffusion.' Coated salt tablets, shaped as disks, were found to swell in deionized water and change shape to an oblate spheroid as a result of the build-up of internal hydrostatic pressure: the change in shape providing a means to measure the 'force' generated. As might be expected, the osmotic force decreased with increasing levels of PEG content. The lower PEG levels allowed water to be imbibed through the hydrated polymer; whilst the porosity resulting from the coating dissolving at higher levels of PEG content (20 to 40%) allowed the pressure to be relieved by the flow of KCl.\textsuperscript{20}

Li developed methods and equations, which by monitoring (independently) the release of two different salts (e.g. KCl and NaCl) allowed the calculation of the relative magnitudes that both osmotic pumping and trans-pore diffusion contributed to the release of salt from the tablet. At low PEG levels, osmotic flow was increased to a greater extent than was trans-pore diffusion due to the generation of only a low pore number density: at a loading of 20%, both mechanisms contributed approximately equally to the release. The build-up of hydrostatic pressure, however, decreased the osmotic inflow, and osmotic pumping. At higher loadings of PEG, the hydrated film was more porous and less resistant to outflow of salt. Hence, although the osmotic pumping increased (compared to the lower loading), trans-pore diffusion was the dominant release mechanism. An osmotic release mechanism has also been reported for microcapsules containing a water soluble core.\textsuperscript{21,22}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure1.5.png}
\caption{Microbeads & Microtubes}
\end{figure}
(C) Chemically Controlled System
* Bioerosion control
* Drug attached to a polymer backbone
* Drug in a biodegradable core
* Drug dispersed in a bioerodible matrix
  – Diffusion controlled
  – Erosion controlled
* Regulated Systems
  – Release varies with environment
  – Externally regulated
* Ultrasound
* Heat
* Magnetic
* Pumps
  – Self regulated
* pH changes
* Bonding to specific lectins
* Triggered devices

![Diagram](image)

**Figure 1.6:** Rate control: Chemical Reaction

(D) Other Systems
(a) Variations on the theme of microspheres.
Kawashima has described methods for the preparation of hollow microspheres ('micro balloons') with the drug dispersed in the sphere's shell, and also highly porous matrix-type microspheres ('micro sponges'). The micro sponges were prepared by dissolving the drug and polymer in ethanol. On addition to water, the ethanol diffused from the emulsion droplets to leave a highly porous particle. Variation of the ratios of drug and polymer in the ethanol solution gave control over the porosity of the particle, and the drug release properties were fitted to the Higuchi model.\textsuperscript{23, 24}

The hollow microspheres were formed by preparing a solution of ethanol/dichloro-methane containing the drug and polymer. On pouring into water, this formed an emulsion containing the dispersed polymer/drug/solvent particles, by a coacervation-type process, from which the ethanol (a good solvent for the polymer) rapidly diffused precipitating polymer at the surface of the droplet to give a hard-shelled particle enclosing the drug, dissolved in the dichloromethane. At
this point, a gas phase of dichloromethane was generated within the particle which, after diffusing through the shell, was observed to bubble to the surface of the aqueous phase. The hollow sphere, at reduced pressure, then filled with water, which could be removed by a period of drying. (No drug was found in the water.) A suggested use of the microspheres was as floating drug delivery devices for use in the stomach.\textsuperscript{25, 26}

**(b) Osmotically Controlled System**

The osmotic pump is similar to a reservoir device but contains an osmotic agent (e.g., the active agent in salt form) which acts to imbibed water from the surrounding medium via a semi-permeable membrane. Such a device, called the 'elementary osmotic pump', has been described by Theeuwes. Pressure is generated within the device which forces the active agent out of the device via an orifice (of a size designed to minimize solute diffusion, whilst preventing the build-up of a hydrostatic pressure head which has the effect of decreasing the osmotic pressure and changing the dimensions (volume) of the device). Whilst the internal volume of the device remains constant, and there is an excess of solid (saturated solution) in the device, then the release rate remains constant delivering a volume equal to the volume of solvent uptake.\textsuperscript{27}

![Figure 1.7: Osmotic drug delivery system](image)

**(c) Pendent devices**

Scholsky and Fitch developed a means of attaching a range of drugs such as analgesics and antidepressants, etc., by means of an ester linkage to poly (acrylate) ester latex particles prepared by aqueous emulsion polymerization. These lattices when passed through an ion exchange resin such that the polymer end groups were converted to their strong acid form could 'self-catalyze' the release of the drug by hydrolysis of the ester link.\textsuperscript{28}

Chafi present a number of papers where drugs have been attached to polymers and also where monomers have been synthesized with a pendent drug attached. The research groups have also prepared their own dosage forms in which the drug is bound to a biocompatible polymer by a labile chemical bond. e.g., polyanhydrides prepared from a substituted anhydride (itself prepared by reacting an acid chloride with the drug: methacryloyl chloride and the sodium salt of methoxy benzoic acid) were used to form a matrix with a second polymer (Eudragit® RL) which released the drug on hydrolysis in gastric fluid. Chafi has also described the use of polymeric Schiff bases suitable for use as carriers of pharmaceutical amines.\textsuperscript{29, 30}
(d) Electrically stimulated release devices
Yuk et al, prepared monolithic devices using polyelectrolyte gels which swelled when, for example, an external electrical stimulus was applied, cause a change in pH. The release could be modulated, by the current, giving a pulsatile release profile.\(^{31}\)

(e) Hydrogels
Hydrogels find a use in a number of biomedical applications, in addition to their use in drug matrices. E.g. soft contact lenses, and various 'soft' implants, etc.\(^{32,33}\)

1.2.4 Mechanisms of drug release from matrix systems
The release of drug from controlled devices is via dissolution or diffusion or a combination of the two mechanisms.

1. Dissolution controlled systems
A drug with slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by the rate of dissolution. In principle, it would seem possible to prepare extended release products by decreasing the dissolution rate of drugs that are highly water-soluble.\(^{34}\)

This can be done by:
* Preparing an appropriate salt or derivative
* Coating the drug with a slowly dissolving material – encapsulation dissolution control
* Incorporating the drug into a tablet with a slowly dissolving carrier – matrix dissolution control (a major disadvantage is that the drug release rate continuously decreases with time).

The dissolution process can be considered diffusion-layer-controlled, where the rate of diffusion from the solid surface to the bulk solution through an unstirred liquid film is the rate-determining step. The dissolution process at steady-state is described by the Noyes-Whitney equation:

\[
\frac{dC}{dt} = \frac{D A (C_0 - C)}{h}
\]

Where,
\[
\frac{dC}{dt} = \text{dissolution rate}
\]
\[
D = \text{the dissolution rate constant (equivalent to the diffusion coefficient divided by the thickness of the diffusion layer D/h)}
\]
\[
C_0 = \text{saturation solubility of the solid}
\]
\[
C = \text{concentration of solute in the bulk solution}
\]
\[
A = \text{Surface area}
\]
\[
h = \text{Diffusion layer thickness}
\]

Equation predicts that the rate of release can be constant only if the following parameters are held constant:
* Surface area
* Diffusion coefficient
Diffusion layer thickness
Concentration difference.

These parameters, however, are not easily maintained constant, especially surface area, and this is the case for combination diffusion and dissolution systems.  

2. Diffusion controlled systems

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. In general, two types or subclasses of diffusional systems are recognized: reservoir devices and matrix devices. It is very common for the diffusion-controlled devices to exhibit a non-zero order release rate due to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds.

Diffusion in matrix devices

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 continues with the interface between the bathing solution and the solid drug moving toward the interior. It follows obviously that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. Derivation of the mathematical model to describe this system involves the following assumptions:

a. A pseudo-steady state is maintained during drug release;
b. The diameter of the drug particles is less than the average distance of drug diffusion through the matrix;
c. The diffusion coefficient of drug in the matrix remains constant (no change occurs in the characteristics of the polymer matrix);
d. The bathing solution provides sink conditions at all times;
e. No interaction occurs between the drug and the matrix;
f. The total amount of drug present per unit volume in the matrix is substantially greater than the saturation solubility of the drug per unit volume in the matrix (Excess solute is present);
g. Only the diffusion process occurs.

In a hydrophilic matrix, there are two competing mechanisms involved in the drug release: Fickian diffusional release and relaxation release. Diffusion is not the only pathway by which a drug is released from the matrix; the erosion of the matrix following polymer relaxation contributes to the overall release. The relative contribution of each component to the total release is primarily dependent on the properties of a given drug.

For example, the release of a sparingly soluble drug from hydrophilic matrices involves the simultaneous absorption of water and desorption of drug via a swelling-controlled diffusion mechanism. As water penetrates into a glassy polymeric matrix, the polymer swells and its glass transition temperature is lowered. At the same time, the dissolved drug diffuses through this swollen rubbery region into the external releasing medium.

This type of diffusion and swelling does not generally follow a Fickian diffusion mechanism. The semi-empirical equation to describe drug release behavior from hydrophilic matrix systems:

\[
Q = k \cdot t^n
\]
Where,

\[ Q = \text{fraction of drug released in time } t, \]
\[ k = \text{rate constant incorporating characteristics of the macromolecular network system and the drug} \]
\[ n = \text{the diffusional exponent. It has been shown that the value of } n \text{ is indicative of the drug release mechanism.} \]

For \( n = 0.5 \), drug release follows a Fickian diffusion mechanism that is driven by a chemical potential gradient. For \( n = 1 \) drug release occurs via the relaxational transport that is associated with stresses and phase transition in hydrated polymers. For \( 0.5 < n < 1 \) non-Fickian diffusion is often observed as a result of the contributions from diffusion and polymer erosion.\(^{37}\)

**Advantages of hydrophilic matrix tablets**

With proper control of manufacturing process, reproducible release profiles are possible. They variability associated with them is slightly less than that characterizing coated release forms. Their capacity to incorporate active principles is large, which suits them to delivery of large doses.

**Disadvantages of hydrophilic matrix tablet**

For a hydrophilic sustained release matrix tablet, in which the release is mainly controlled by erosion of the swollen polymer gel barrier at the tablet surface, the presence of food may block the pores of the matrix and inhibit the drug release rate.
Figure 1.8: Drug release from hydrophilic matrix tablet

The hydrophilic polymers can be arranged into three broad categories:

(A) Non-cellulose natural or semi synthetic polymer
These are products of vegetable origin and are generally used as such. Agar, alginate, guar gum, chitosan, modified starches, are commonly used polymer.

(B) Polymers of acrylic acid
These are arranged in carbomer group and commercialized under the name of carbopol. The major disadvantage of this type of polymer is its pH dependent gelling characteristics.

(C) Cellulose ether
This group of semi-synthetic cellulose derivatives is the most widely used group of polymer. Non-ionic such as Hydroxypropylmethylcellulose (HPMC) of different viscosity grades are widely used group of polymers. Non-ionic such as HPMC of different viscosity grades is widely used.

3. Bioerodible and combination of diffusion and dissolution systems
Strictly speaking, therapeutic systems will never be dependent on dissolution or diffusion only. In practice, the dominant mechanism for release will overshadow other processes enough to allow classification as either dissolution rate-limited or diffusion-controlled release. As a further complication these systems can combine diffusion and dissolution of both the drug and the matrix material. Drugs not only can diffuse out of the dosage form, as with some previously described matrix systems, but also the matrix itself undergoes a dissolution process. The complexity of the system arises from the fact that as the polymer dissolves the diffusion path length for the drug may change. This usually results in a moving boundary diffusion system. Zero-order release is possible only if surface erosion occurs and surface area does not change with time.

Swelling-controlled matrices exhibit a combination of both diffusion and dissolution mechanisms. Here the drug is dispersed in the polymer, but instead of an insoluble or non-erodible polymer, swelling of the polymer occurs. This allows for the 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 and drug solubility. This system usually minimizes burst effects, as rapid polymer swelling occurs before drug release.

With regards to swellable matrix systems, different models have been proposed to describe the diffusion, swelling and dissolution processes involved in the drug release mechanism. However the key element of the drug release mechanism is the forming of a gel layer around the matrix, capable of preventing matrix disintegration and further rapid water penetration. The gel strength is important in the matrix performance and is controlled by the concentration, viscosity and chemical structure of the rubbery polymer. This restricts the suitability of the hydrophilic polymers for preparation of swellable matrices. Polymers such as carboxymethyl cellulose, hydroxypropyl cellulose or tragacanth gum, do not form the gel layer quickly. Consequently, they are not recommended as excipients to be used alone in swellable matrices.
The swelling behavior of heterogeneous swellable matrices is described by front positions, where ‘front’ indicates the position in the matrix where the physical conditions sharply change. Three fronts are present, as shown in Figure 1.9.  
* The ‘swelling front’ clearly separates the rubbery region (with enough water to lower the T\textsubscript{g} below the experimental temperature) from the glassy region (Where the polymer exhibits a T\textsubscript{g} that is above the experimental temperature).
* The ‘erosion front’, separates the matrix from the solvent. The gel-layer thickness as a function of time is determined by the relative position of the swelling and erosion moving fronts.
* The ‘diffusion front’ located between the swelling and erosion fronts, and constituting the boundary that separates solid from dissolved drug, has been identified.
* During drug release, the diffusion front position in the gel phase is dependent on drug solubility and loading. The diffusion front movement is also related to drug dissolution rate in the gel.

![Figure 1.9: The fronts in a swellable HPMC matrix](image)

### 1.2.5: FACTORS INFLUENCING THE DRUG RELEASE FROM MATRIX:

- Choice of matrix material.
- Amount of drug incorporated in the matrix.
- Viscosity of the hydrophilic material in aqueous system at a fixed concentration.
- Drug: matrix ratio.
- Tablet hardness, porosity, and density variation.
- Entrapped air in tablet.
- Tablet shape and size.
- Drug particle size.
- Solubility of drug in aqueous phase.
Surfactants and other additives.

1.4: FACTORS INFLUENCING DESIGN OF SUSTAINED DRUG DELIVERY SYSTEMS

1. Biological factors

A) Biological half-life:
Therapeutic compounds with short half-lives are excellent candidates for sustained-release preparations, since this can reduce dosing frequency.45, 46

B) Absorption:
The absorption rate constant is an apparent rate constant, and should, in actuality, be the release rate constant of the drug from the dosage form. If a drug is absorbed by active transport, or transport is limited to a specific region of the intestine, sustained-release preparations may be disadvantageous to absorptions.45, 46

C) Metabolism:
Drugs that are significantly metabolized before absorption, either in the lumen or tissue of the intestine, can show decreased bioavailability 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 the drug to its metabolite.45, 46

D) Dosage form Index:
It is defined as the ratio of $C_{ss, max.}$ to $C_{ss, min}$. Since the goal of controlled release formulation is to improve therapy by reducing the dosage form index while maintaining the plasma drug levels within the therapeutic window, ideally its value should be as close to one as possible.46

2. Physicochemical factors

A) Dose Size:
In general, single dose of 0.5 – 1.0 g is considered maximal for a conventional dosage form. This also holds true for sustained-release dosage forms. Another consideration is the margin of safety involved in administration of large amounts of drug with a narrow therapeutic range.

B) Ionization, pKa and aqueous solubility:
Most drugs are weak acids or bases. Since the unchanged form of a drug preferentially permeates across lipid membranes, it is important to note the relationship between the pKa of the compound and the absorptive environment. Delivery systems that are dependent on diffusion or dissolution will likewise be dependent on the solubility of drug in the aqueous media. For dissolution or diffusion sustaining forms, much of the drug will arrive in the small intestine in solid form, meaning that the solubility of the drug may change several orders of magnitude during its release. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1 mg/ml.

C) Partition coefficient:
Compounds with a relatively high partition coefficient are predominantly lipid-soluble and, consequently, have very low aqueous solubility. Furthermore these compounds can usually persist in the body for long periods, because they can localize in the lipid membranes of cells.
D) Stability:
Orally administered drugs can be subjected to both acid-base hydrolysis and enzymatic degradation. For drugs that are unstable in the stomach, systems that prolong delivery over the entire course of transit in the GI tract are beneficial. Compounds that are unstable in the small intestine may demonstrate decreased bioavailability when administered from a sustaining dosage form.45,46

E) Molecular Weight of the Drug:
The lower the molecular weight, the faster and more complete the absorption. The upper limit of drug molecular size for passive diffusion is 600 Daltons. Drugs with large molecular size are poor candidates for oral controlled release systems e.g. peptides and proteins.

F) Mechanism and Site of Absorption:
Drugs absorbed by carrier mediated transport processes and those absorbed through a window are poor candidates for controlled release systems e.g. several B vitamins.

G) Biopharmaceutic Aspects of Route of Administration:
Oral and parenteral (i.m.) routes are most popular followed by transdermal application.

2. Pharmacodynamic Characteristics of the Drug

A) Therapeutic Range:
A candidate drug for controlled delivery system should have a therapeutic range wide enough such that variations in the release rate do not result in a concentration beyond this level.

B) Therapeutic Index (TI):
The release rate of a drug with narrow therapeutic index should be such that the plasma concentration attained is within the therapeutically safe and effective range.

C) Plasma Concentration-Response Relationship:
Drugs such as reserpine whose pharmacologic activity is independent of its concentration are poor candidates for controlled release systems.

1.4.1: Drug selection for oral sustained release drug delivery systems
The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug form the G. I. tract, the general absorbability, the drug’s molecular weight, solubility at different pH and apparent partition coefficient.45,46
Table 1.1: Physicochemical Parameters for drug selection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preferred value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight/ size</td>
<td>&lt; 1000 Daltons</td>
</tr>
<tr>
<td>Solubility</td>
<td>&gt; 0.1 mg/ml for pH 1 to pH 7.8</td>
</tr>
<tr>
<td>Apparent partition coefficient</td>
<td>High</td>
</tr>
<tr>
<td>Absorption mechanism</td>
<td>Diffusion</td>
</tr>
<tr>
<td>General absorbability</td>
<td>From all GI segments</td>
</tr>
<tr>
<td>Release</td>
<td>Should not be influenced by pH and enzymes</td>
</tr>
</tbody>
</table>

The pharmacokinetic evaluation requires knowledge on a drug’s elimination half-life, total clearance, absolute bioavailability, possible first-pass effect, and the desired steady concentrations for peak and trough. \( t_{1/2}, 45 \)

Table 1.2: Pharmacokinetic parameters for drug selection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination half life</td>
<td>Preferably between 0.5 and 8 h</td>
</tr>
<tr>
<td>Total clearance</td>
<td>Should not be dose dependent</td>
</tr>
<tr>
<td>Elimination rate constant</td>
<td>Required for design</td>
</tr>
<tr>
<td>Apparent volume of distribution ( V_d )</td>
<td>The larger ( V_d ) and MEC, the larger will be the required dose size.</td>
</tr>
<tr>
<td>Absolute bioavailability</td>
<td>Should be 75% or more</td>
</tr>
<tr>
<td>Intrinsic absorption rate</td>
<td>Must be greater than release rate</td>
</tr>
<tr>
<td>Therapeutic concentration ( C_{ss, av} )</td>
<td>The lower ( C_{ss, av} ) and smaller ( V_d ), the loss among of drug required</td>
</tr>
<tr>
<td>Toxic concentration</td>
<td>Apart the values of MTC and MEC, safer the dosage form. Also suitable for drugs with very short half-life.</td>
</tr>
</tbody>
</table>

1.5: DRUG RELEASE PATTERNS OF SUSTAINED RELEASE DOSAGE FORMS

If one assumes that-
1. Drug disposition follows first-order kinetics.
2. The rate-limiting step in the absorption is rate of drug release from the controlled release formulation (i.e. \( K_r < K_a \)), and
3. The released drug is rapidly and completely absorbed.

Then, the four models for drug input based on the drug release pattern can be defined:
1. Slow zero-order release.

![Figure 1.10: Slow zero-order](image)

2. Slow first-order release

![Figure 1.11: Slow first-order](image)

3. Initial rapid release of loading dose followed by slow zero-order release.

![Figure 1.12: Initial rapid dose then zero-order](image)
4. Initial rapid release of loading dose followed by slow first-order release.

![Graph showing initial rapid dose then slow first-order release](image)

**Figure 1.13:** Initial rapid dose then slow first-order

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-

- Behavior of drug within its delivery systems
- Behavior of the drug and its delivery system jointly in the body.

The first of the two elements basically deal with the inherent properties of drug molecules, which influence its release from the delivery system. For conventional systems, the rate-limiting step in drug availability is usually absorption of drug across a biological membrane such as the gastrointestinal wall. However, in sustained/controlled release product, the release of drug from the dosage form is the rate limiting instead; thus, drug availability is controlled by the kinetics of drug release than absorption.37

**1.6: BIOAVAILABILITY TESTING OF SUSTAINED RELEASE FORMULATIONS**

The purpose of *in vivo* bioavailability study on a sustained release formulation is to determine-

1. The fraction of drug absorbed (should ideally be greater than or equal to 80% of sustained release dosage form).
2. Occurrence of dose dumping.
3. Influence of food as well as circadian effect on drug absorption.
4. The time period for which the plasma concentration stays within the therapeutic range i.e. therapeutic occupancy time.
5. $C_{\text{max}}/C_{\text{min}}$ ratios at steady state.
6. Percent fluctuation calculated from equation:

\[100 \times \frac{(C_{\text{max}} - C_{\text{min}})}{C_{\text{ss}}}\]

**CONCLUSION**

The Sustained release drug delivery system is very helpful in increasing the efficiency of the dose, safety of dose as well as the patient compliance. Nowadays, the oral route of administration for Sustained release drug delivery system has received more attention due to its more flexibility, reduced dosing frequency and better patient compliance. The design of oral Sustained release drug delivery system depends on various factors like, physic-chemical properties of drug, type of delivery system, disease being treated, patient condition, treatment duration, presence of food,
gastrointestinal motility and co-administration of other drugs. From the above discussion, we can concluded that Moreover; the reasonable cost of oral Sustained release drug delivery system has lead ease of market penetration as replacement of oral conventional drug delivery system.

REFERENCES