CHAPTER - II

CONTROLLED RELEASE DRUG DELIVERY SYSTEMS
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The ways in which chemicals or drugs are administered have gained increasing attention in the past two decades. Normally, a chemical is administered at a given dose at a given time only to have to repeat that dose several hours or days later. This is not economical and sometimes results in damaging side effects. As a consequence, increasing attention has been focused on methods of giving drugs continually for prolonged time periods and in a controlled fashion. The primary method of accomplishing this controlled release has been through incorporating the chemicals within polymers. This technology now spans many fields and includes pharmaceutical, food and agricultural applications, pesticides, cosmetics, and household products.

Oral route has been one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage forms. Most conventional dosage forms for oral delivery, such as tablets and capsules, are formulated to release the active drug immediately after administration to obtain rapid and complete systemic drug absorption. In recent years various modified drug products have been developed to release the active drug from the product at a controlled rate\(^1\).
**Sustained Release Technology**

**Principle of Sustained Release Systems**

Sustained or controlled release system is a system that delivers an agent at a controlled rate for an extended time. It might localize drug action by spatial placement near where it is needed or it might target drug action by using techniques to deliver drug to a particular cell type. The terms controlled release and sustained release are often observed to be used interchangeably. However there is difference in the depth of the concept they carry. In sustained release, a pharmaceutical dosage form is formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed or prolonged and its plasma profile is sustained in duration. In other words, the drug’s release is simply extended in time i.e. the rate and duration are not designed to achieve a particular profile. But the controlled release concept goes beyond the scope of sustained drug action. It implies a predictability and reproducibility in drug release kinetics. A controlled delivery is a well-characterized and reproducible dosage form. Such a system controls entry to the body according to the specifications of the required drug delivery profile. In other words, rate and duration of delivery are designed to achieve desired concentration\(^2\). However in this paper the words are used interchangeably.

The drug release from conventional dosage forms is characterized by periodic administration, non-specific administration, and high systemic
concentrations leading to toxicity causing side effects or damage to organs. Additionally low concentrations (that occur in between two successive doses) can be ineffective. Where as in sustained/controlled release dosage forms the drug concentrations rises quickly to effective level and this effective concentration is maintained for extended time as shown in Figure 2.1\(^3\).

![Drug levels in the blood with (a) traditional drug dosing and (b) Sustained or controlled –delivery dosing](image)

**Fig 2.1.** Drug levels in the blood with (a) traditional drug dosing and (b) Sustained or controlled –delivery dosing\(^3\).

The conventional delivery is clearly disadvantageous that it is inconvenient, difficult to monitor, large amounts of drug can be “lost” when they don’t get to the target organ, drug goes to non-target cells and can cause damage and it is expensive as more drug than necessary is used. To the contrary in sustained/controlled release systems we have reproducible
rate, prolonged deliver, less frequent administration of which as a result better patient compliance and increased convenience is achieved, reduced side effects because effective concentration is maintained, and if targeting is achieved it can eliminate damage to non-target organs, less drug used, the possibility of re-patenting without new drug development and also economic advantages by virtue of more efficient dosage, at the expense of possibly more complicated fabrication.

**Advantages of Controlled Release Systems:**

They provide one or more of the following benefits or advantages.

1. Controlled administration of a therapeutic dose at a desirable delivery rate.
2. Maintenance of plasma drug concentration within an optimal therapeutic range for prolonged duration of action.
3. More consistent and prolonged therapeutic effect is observed.
5. Reduction of adverse side effects.

**Disadvantages of Controlled Release Dosage Forms:**

1. Toxicity due to dose dumping occurs when more than usual fraction of dose is being released.
2. Increased cost.
Design Parameters:

Selection of route of administration depends on many factors such as drug properties, disease state being treated, age and condition of the patient. For the oral route of administration, there are many properties that must be considered. They include pH, enzyme content, temperature, protein content, food content, and general state of health.

Biological Factors influencing Oral Sustained – Release dosage form design:

Biological Half Life:

Therapeutic compounds with short half lives are excellent candidates for sustained release preparations. Drugs with very short half lives will require excessively large amounts of drug in each dosage unit to maintain sustained effects. Thus forcing the dosage form itself to become too large to be administered. Compounds with relatively long half lives, generally greater than 8 hours, are generally not used in sustaining forms since their effect is already sustained and also GI transit time is 8 to 12 hr. 4

Absorption:

The characteristics of absorption of drug absorption of a drug can greatly affect its suitability as a sustained release product. Assuming the transit time of most drugs and devices in the absorptive regions before release is complete. The absorption rate constant is an apparent rate
constant\textsuperscript{4}. It should in actuality be the release rate constant of the drug form dosage form.

Attempts to retain these dosage forms within the stomach include two approaches. One is to formulate low density pellets or capsules, which float on gastric juice, delaying their transfer out of stomach\textsuperscript{5,6}. Another approach is using bio-adhesive materials\textsuperscript{7}. This would allow extension of the residence time. Drugs with specific "Windows" for absorption such as riboflavin could be given successfully as a sustained release preparation.

**Metabolism:**

Drugs that are significantly metabolized especially in the region of the small intestine can show decreased bioavailability from slower releasing dosage forms. This is due to saturation of intestinal wall enzyme systems.

**Physico-Chemical factors influencing Oral Sustained Release dosage form:**

**Dose Size:**

For orally administered, systems, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5 to 1gm is considered maximal\textsuperscript{8}.

**Ionization, P\textsuperscript{Ka} and Aqueous Solubility:**

The pH – Partition hypothesis simply states that the unchanged form of a drug species will be preferentially absorbed through many body tissues. Therefore it is important to note the relationship between P\textsuperscript{Ka} of the compound and its absorptive environment. For many compounds the site of
maximum absorption will also be the area in which the drug is least soluble. For conventional dosage forms the drug can generally fully dissolve in the stomach and then be absorbed in the alkaline pH of the intestine. For dissolution or diffusion sustaining forms, much of the drug will arrive in the small intestine in solid form. This means that the solubility of the drug is likely to change several orders of magnitude during its release.

Compounds with very low solubility are inherently sustained since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug. The lower limit for the solubility of a drug to be formulated in a sustained – release system has been reported to be 0.1mg/ml\(^9\). Thus, for slightly soluble drugs, diffusional systems will be poor choice since the concentration in solution will be low.

**Partition coefficient:**

The compounds with a relatively high partition coefficient are predominantly lipid soluble and easily penetrate membranes resulting high bioavailability\(^{10}\). Compounds with very low partition coefficient will have difficulty in penetration of membranes, resulting poor bioavailability. Further more partitioning effects apply equally to diffusion through polymer membranes.

**Stability:**

For drugs that are unstable in stomach, systems that prolong delivery over entire GI tract are beneficial. Compounds that are unstable in the small
intestine may demonstrate decreased bioavailability when administered as a sustained release dosage form.

The most serious restriction to the use of oral sustained release dosage forms would be the limited residence time of the dosage form in the small intestine (i.e. 8-12hrs.)

There are a number of methods to prolong the drug activity in the body ranging from chemical alteration of the drug, to placement of the drug in rate controlling dosage form.

Majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms to generate slow release of drug. Both mechanisms operate in a given dosage form usually one mechanism will predominate the other.

CLASSIFICATION OF CONTROLLED SYSTEM:

Sustained oral products employing dissolution as the rate limiting step, are in principle simplest to prepare. Even 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.

We can assume the dissolution process, where the rate of diffusion from the solid surface to the bulk solution through a liquid film which is the rate limiting step. In this case, the dissolution process at steady state would be described by the Noyes – Whitney equation.

\[
\frac{dc}{dt} = K_d A (C_s - C) \quad \text{………………………(1)}
\]
\[ \frac{dc}{dt} \] is the dissolution rate, \( K_D \) is the dissolution rate constant, \( C_S \) is the saturation solubility of the drug and \( C \) is the concentration of drug in the bulk of the solution. In relation to diffusion expression that \( K_D \) equals \( D/VL \). Where \( D \) is the diffusion coefficient, \( L \) is the thickness of the unstirred liquid film and \( V \) is the Volume of the dissolution medium.

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

The common forms of dissolution control formulations fall into two categories.

(a) Encapsulation dissolution control.
(b) Matrix dissolution control.

**Encapsulation dissolution control:**

These methods generally involve coating individual particles or granules of drug with a slowly dissolving material. The coated particles can be compressed directly into tablets as in space tabs or placed in capsules as in spansules products. Since the time required for dissolution of the coat is a function of thickness and aqueous solubility one can obtain repeat or
sustained action by employing a narrow or a wide spectrum of coated particles of varying thickness respectively.

**Matrix dissolution Control:**

This method involve compressing the drug with a slowly dissolving carrier into 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 hydrophobic additives, the wettability of tablet and particle surface.

**Diffusion Controlled Release:**

Diffusion controlled sustained release products are basically of two types\textsuperscript{11}.

(1) Encapsulated Diffusion Control.

(2) Matrix Diffusion Control.

(1) **Encapsulated Diffusion Control:**

In this system water insoluble polymeric material encases a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particles or tablet. The rate of drug release is given by equation.

\[
\frac{dm}{dc} = \frac{\Delta D K \Delta C}{L} \quad \text{------------------------(3)}
\]

Where 'A' is area, D is diffusion coefficient, K is the partition coefficient of the drug between the membrane and drug core, L is the diffusional path length and \( \Delta C \) 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 drug in the core. If the partition coefficient is high, the core will be depleted of drug in a short time, so that zero order release will be observed only over a short segment of the time course of drug release.

To obtain a constant drug release rate all the terms in right hand side of the above equation must be held constant.

Methods to develop reservoir type devices include press coating, air suspension coating techniques\textsuperscript{12}. Microencapsulation process is a commonly used procedure to coat the drug particles to be incorporated.

\textbf{(2) Matrix Diffusion Control:}

In this type a solid drug is dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution. The equation describing drug release from this system has been derived by Higuchi \textsuperscript{13,14}.

\[ Q = \left\{ \left( \frac{DE}{T} \right) \left( 2A - EC_s \right) C_{S} \right\}^{1/2} \]  

\( Q \) = Weight in grams of drug released per unit area of surface at time 't'.

\( D \) = Diffusion coefficient.

\( E \) = Porosity of matrix.

\( C_s \) = Solubility of drug in the release medium.

\( T \) = Tortuosity of the matrix.

\( A \) = Concentrations of drug in the tablet expressed as gm/ml.
The assumptions made in deriving above equation are:

1. A pseudo steady state is maintained during release.
2. \( A >> C_s \); i.e. excess solute is present.
3. \( C = 0 \) in solution at all times (Perfect sink).
4. Drug particles are much smaller than those of matrix.
5. The diffusion coefficient remains constant.
6. No interaction occurs between the matrix and drug\(^{15}\).

For the purposes of data treatment, the above equation is usually reduced to

\[
Q = Kt^{\frac{1}{2}} \quad \text{------------------------ (5)}
\]

Where \( K \) is a constant, so that a plot of amount of drug released versus the square root of time should be linear if the drug is diffusion controlled.

Depending on the properties of the matrix and the polymer system, deviation from constant release can occur. For example, in the case of insoluble matrix the drug may have to diffuse through tortuous pathway to reach the bulk solution. To account for this a tortuosity correction factor is added to the release equation. With polymer encapsulated systems swelling or corrosion of the membrane will lead to changes in drug release rate.

The most popular drug delivery system has been the matrix system containing uniformly dissolved or dispersed drug such as tablets and granules, because of its ease of fabrication. However, the release behaviour is inherently first order in nature with continuously diminishing release rate.
for all three standard geometrics: slab, cylinder and sphere. This is the result of increase in diffusional resistance and a decrease in effective area at the diffusion front as drug release proceeds. Use of zero order delivery systems will optimize the therapy by maintaining drug concentration for prolonged periods.

Methods of altering the kinetics of drug release from the inherent first order behaviour to zero order have involved the use of geometry factors, erosion dissolution control and swelling control mechanisms, non-uniform drug loading and matrix – membrane combinations.

Swelling phenomena is generally encountered in both hydrophilic and hydrophobic polymer matrices during the release of entrapped water soluble drugs in an aqueous environment. The release of water soluble drugs from initially dehydrated hydrogels generally involves the simultaneous absorption of water and desorption of drug via a swelling controlled diffusion mechanism. This involves a moving diffusional front separating an undissolved core from a partially extracted region and swelling polymer front. As a consequence of swelling, chain relaxation take place there by releasing drug. In case of glassy polymers relaxation is time dependent. This is the source of deviation from Fick's law.

In case, where the sorption process is completely governed by the rate of polymer relaxation, the so called case II transport, characterized by a linear time dependence in both the amount diffused and the penetrating swelling front position results. In most systems the intermediate situation
which is often termed non-Fickian or anomalous diffusion will prevail wherever the rates of diffusion and polymer relaxation are comparable.

By Korsemeyer and Peppas\textsuperscript{16} equation one can express the fraction released $M_t/M_\infty$ as a power function of time $t$ for the short time period.

$$\frac{M_t}{M_\infty} = K't^n$$  \hspace{1cm} (6)

Where $K'$ is a constant characteristic of the system and $n$ is an exponent characteristic of the mode of transport. For $n = 0.5$, the drug release follows the well known Fickian diffusion mechanism. For $n > 0.5$ non-Fickian or anomalous diffusion behaviour is generally observed. The special case of $n = 1$ describes a case II transport mechanism. The drug release from such devices having constant geometry will be constant rate (zero order).

Usually “non Fickian” release is observed till the polymer chains rearrange to an equilibrium state. Once the hydrogel matrix is significantly hydrated, drug release becomes Fickian.

The relative importance of relaxation and diffusion can in principle be estimated with the Deborah number, $De$\textsuperscript{17} which is the ratio of characteristic relaxation time $\lambda$ to a characteristic diffusion time $\theta$. ($\theta = L^2/D$) Where $L =$ Length).

$$De = \frac{\lambda}{\theta}$$ \hspace{1cm} \text{(7)}

When $De \ll 1$ relaxation is much faster than diffusion and Fickian diffusion is observed. This occurs well above the transition temperature $T_g$. 
where gels are rubbery and the diffusion coefficient $D$ is generally a strong function of concentration. When $D \approx 1$ relaxation and diffusion interact leading to complex transport behaviour that is termed as "non-Fickian").

**Types of Sustained Release Systems**

Numerous oral sustained release systems have been developed among which some are listed in Table 2.1. They can be classified by type of device and rate controlling mechanism. There are three primary mechanisms by which active agents can be released from a delivery system: diffusion through a matrix, diffusion through a polymeric membrane, and swelling (solvent activation) followed by diffusion. Any or all of these mechanisms may occur in a given release system. Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. The diffusion can occur on a macroscopic scale—as through pores in the polymer matrix—or on a molecular level, by passing between polymer chains$^{18}$.

**Table 2.1** Types of device and rate controlling mechanisms of some of the oral sustained release systems$^{18}$.

<table>
<thead>
<tr>
<th>Types of device</th>
<th>Mechanisms</th>
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<tbody>
<tr>
<td>Matrix</td>
<td>Diffusion (through a matrix)</td>
</tr>
<tr>
<td>Reservoir/Membrane</td>
<td>Diffusion through a polymeric membrane</td>
</tr>
<tr>
<td>Osmotic Pumps</td>
<td>Solvent activation and the resultant osmotic pressure developed.</td>
</tr>
<tr>
<td></td>
<td>Osmotic pump or polymer swelling</td>
</tr>
</tbody>
</table>
**Monolithic (Matrix) systems**

Matrix systems are the simplest and cheapest devices. In such systems the active agent is physically blended with the polymer in dissolved or dispersed form to obtain a homogeneous system. The release mechanism from matrix devices is figuratively shown below in Figure 1.2. Diffusion occurs when the drug passes from the polymer matrix into the external environment. As the release continues, its rate normally decreases with this type of system, since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to be released.

![Figure 2.2](image)

**Figure 2.2.** Drug delivery from a typical matrix drug delivery 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
no 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. Generally, the drug is present in a smaller percent, so that the matrix gives extended protection against water and the drug diffuses out slowly over time. Most matrix materials are water insoluble, although some may swell slowly in water. Matrix type of drug release may be manufactured into a tablet or small beads depending on the formulation composition.

The drug release properties of monolithic devices may be dependent upon the solubility of the drug in the polymer matrix or, in the case of porous matrices, 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 are filled with fluid from the environment increasing the rate of release of the drug.

**Oral Hydrophilic Matrix Systems**

One common method of fabricating sustained/controlled-release formulations is by the incorporation of the drug in a matrix containing a
hydrophilic, rate-controlling polymer. The popularity of hydrophilic polymers is due to the several advantages they provide. Their capacity to incorporate active principles is large which is suitable for the delivery of large doses and also reproducible release profiles are achievable with proper control of the manufacturing process. Though the structure makes the immediate release of a small amount of active principle unavoidable, there is no risk of releasing of large part of the dose. Moreover when properly formulated and compressed hydrophilic matrices can be very suitable and readily manufactured dosage forms for the sustained release of drugs. The manufacturing processes are relatively straightforward. The usual route of formulating the tablets is based on the established tabletting technology of manufacturing.\(^{20}\)

**Drug Release Mechanism from Hydrophilic Matrices**

The drug release from hydrophilic matrix systems is said to be a complex interaction of swelling, diffusion, and erosion processes. When the dosage form comes in contact with water, partial hydration of the polymer takes place resulting in the formation of a layer of gel. As the water penetrates the system at a rate, which depends to a large extent on the nature of the polymer, the gel layer expands by getting thicker. At the same time, there by now completely hydrated outer layers start to disperse via an attrition process which, furthermore, means the process of water penetration can continue until the system is completely dispersed. Therefore, the release of an active principle by a hydrophilic matrix system is produced by
two simultaneous mechanisms (i) erosion or attrition of the outermost, least consistent gel layers, and (ii) dissolution of the active principle in the liquid medium and diffusion through the gel barrier when formed\textsuperscript{21}.

The mechanism which dominates is directly related to the hydrosolubility of the active principle. When this is very low, the possibility of release by diffusion will be practically zero and release will be almost all by surface erosion, giving profiles characteristic of zero order kinetics. If the drug is moderately or highly hydrosoluble, the mechanism governing release will be diffusion\textsuperscript{22}. Three stages can be cited in the overall diffusion-ruled release process.

Firstly the water dissolves the active principle at the surface, causing its immediate release. The water penetrates the matrix through the pores and gives rise to the gelling of the polymer. The rate of penetration in the first stage depends on the porosity of the system and the gel formed does not necessarily constitute a continuous layer, particularly when the polymer particles are relatively large. In the second stage, or stationary phase, occupying 60-70\% of the process, the water is continuously penetrating the system, at the same time as the gel is expanding.

During this phase, release is controlled by the diffusion process and not by dissolution of the active principle or penetration of water. Lastly the tailing-off period starts when the water reaches the centre of the system and the concentration of the drug falls below the solubility value. This final stage is characterized by a reduction in the release rate\textsuperscript{23}. 

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Despite the great complexity of the process, data for the release of hydrosoluble active principles from hydrophilic matrices is normally interpreted using the relatively simple Higuchi model\textsuperscript{24}. This equation which assumes active principle dissolution and diffusion through the water filling the pores in “sink” conditions, predicts linear plots of quantity of percentage released against the square-root of time.

From the above, it is clear that the hydro solubility of the active principle plays an important part in the release mechanism. However, solubility is not the only physiochemical characteristic that affects the release mechanism but the hydrosoluble active principle’s capacity to diffuse through the gel barrier may also be worth considering. In certain cases, the usual linear dependence of the fraction of hydrosoluble active principle released on the square root of time is not observed. To interpret these profiles, it is necessary to look closely at the release process, taking into consideration the effects of the structural changes the polymer undergoes as it swells, including alterations in the mobility of the polymer chains, macromolecular relaxations and changes in the porous structure regarding both the mean pore size and the pore size distribution. Hence, as the swelling process progresses, diffusion of the active principle will not only be via the water-filled pores, but also via the polymer chains, the incidence of the latter depending on the polymer’s physical structure, its density of reticulation and its degree of crystallinity and also on the possible solute-polymer interactions \textsuperscript{25,26}.
Korsemeyer et al\textsuperscript{27} have proposed a semi empirical formula capable of revealing and identifying behaviors which are not usual or Fickian:

\[ \frac{M_t}{M_\infty} = K t^n \]  (Equation 8)

Where \( \frac{M_t}{M_\infty} \) is the fraction release of drug at time \( t \), \( K \) is a kinetic constant characteristic of the drug/polymer system and \( n \) is the diffusional or release exponent indicative of the mechanism of drug release.

Among the hydrophilic polymers, cellulose ethers are the polymers of choice and the most commonly used for oral sustained release formulations. This is in part because of their relative abundance, low cost and ease of fabrication\textsuperscript{28}. HPMC, which is the most widely used polymer in the formulation of sustained/controlled release matrix formulations, is employed as a matrix forming agent in this project.

**Properties for selection of a drug for sustained release formulation:**

<table>
<thead>
<tr>
<th>Physico-Chemical Factors of Drug</th>
<th>Factor</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Size</td>
<td>Less than one gram</td>
<td></td>
</tr>
<tr>
<td>Solubility &amp; ( pK_a )</td>
<td>Very soluble low soluble drugs</td>
<td></td>
</tr>
<tr>
<td>Partition Coefficient</td>
<td>High, Low</td>
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</tr>
<tr>
<td>Drug Stability</td>
<td>Gastro Intestinal pH</td>
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<table>
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<th>Factor</th>
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<td>Absorption</td>
<td>No Absorption Window</td>
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</tr>
<tr>
<td>Metabolism</td>
<td>Intestinal First Pass</td>
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References


