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1.1 Introduction to sustained release

Drugs are rarely administered as pure chemical substances alone and are always given as formulated preparations or medicines (i.e. drug delivery systems or dosage forms). These can vary from relatively simple solutions to complex drug delivery systems through the use of appropriate additives or excipient in the formulations. It is the formulation additives that, modify solubility, suspend, thicken, preserve, emulsify, modify dissolution, improve the compressibility and flavor drug substances to form various acceptable preparations or dosage forms. Before a drug substance can be successfully formulated into a dosage form, many factors must be considered. These can be broadly grouped into the following three categories [1].

- Biopharmaceutical considerations, including factors affecting the absorption of the drug substance from different administration routes;
- Drug factors, such as the physical and chemical properties of the drug substance;
- Therapeutic considerations, including consideration of the clinical indication to be treated and patient factors.

High-quality and efficacious medicines will be formulated and prepared only when all these factors are considered and related to each other. This is the underlying principle of dosage form design [1].

The oral route of drug administration is the most important method of administering drugs for systemic effects. The goal of any drug delivery system is to provide a therapeutic amount of drug to proper site(s) in the body to achieve promptly and then maintain the desired drug concentration. The drug delivery system should deliver a drug at a rate dictated by the needs of the body over a specified period of treatment.
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This idealized objective points to the two aspects most important to drug delivery, namely spatial placement and temporal delivery of a drug. Spatial placement relates to targeting of a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. A bulk of research has been directed at oral dosage forms that satisfy temporal aspect of drug delivery, since many drugs require constant ‘drug blood levels’ within therapeutic range for the required duration of action to be effective [2,3].

1.1.1 Conventional drug delivery system

The oral route of drug administration is perhaps the most appealing route for the delivery of drugs. Of the various dosage forms administered orally, the tablet is one of the most preferred dosage forms because of its ease of manufacturing, convenience in administration, accurate dosing, stability compared with oral liquids, and because it is more tamperproof than capsules. The gastrointestinal tract provides sufficient fluid to facilitate disintegration of the dosage form and dissolution of the drug. The large surface area of gastric mucosa favors the drug absorption. Therefore, the oral route has continued to be the most appealing route for drug delivery despite the advancements made in the new drug delivery systems. Banker and Anderson stated that at least 90% of drugs used to produce systemic effect are administered orally. The bioavailability of drug is dependent on in vivo disintegration, dissolution, and various physiological factors. In recent years, scientists have focused their attention on the formulation of quickly disintegrating tablets. The task of developing rapidly disintegrating tablets is accomplished by using a suitable diluents and superdisintegrant.
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Conventional dosage forms of a drug such as tablets, capsules, solution, suspension, suppository etc. releases the active ingredients into the absorption pool immediately. The drug level time profile of such a system is as shown in Fig.1.1.1

![Figure 1.1.1 Typical drug blood level versus time profiles for intravenous injection and an extra vascular route of administration. [2]](image)

As seen in the Fig. 1.1.1 administration of drug either by intravenous injection or an extra vascular route, for e.g., orally, intramuscular or rectally administration of the conventional dosage form does not maintain the drug blood levels within the therapeutic range for an extended period of time. Here, the release of drug is much faster than the absorption (Kr >> Ka). The short duration of action is due to the inability of conventional dosage form to control temporal delivery.

One approach to maintain drug blood levels in the therapeutic range for longer periods, for e.g., increasing the initial dose of an intravenous injections, toxic levels may be produced at early times. This approach is undesirable and unsuitable. An alternate approach is to administer the drug repetitively using a constant dosing interval, as in multiple dose therapy. This result are shown in Fig.1.1.2

The Sustained Delayed Release of Anti-inflammatory Drugs 3
Figure 1.1.2 Typical blood level versus time profiles following oral multiple dose therapy [2].

The concentration of a drug in the blood fluctuates over successive doses of most conventional single unit oral dosage forms. The main reason for this is that the drug is released immediately after administration (i.e. burst release effect). This causes the drug blood concentration to rise quickly to a high value ("peak") followed by a sudden decrease to a very low level ("trough") as a result of drug elimination [2, 6].

The potential problems associated with multiple dose therapy are:

1. If the dosing interval is not appropriate for the biological half-life of the drug, large 'peaks' and 'valleys' in the drug blood level may result. For e.g., drugs with short half-lives require frequent dosing to maintain therapeutic levels.

2. The drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease states.
3. Patient non-compliance with the multiple-dosing regimen can result in failure of this approach.

In many instances, the potential problems associated with conventional drug therapy can be overcome by multiple dosing. However, these problems are significant enough to make drug therapy with conventional dosage forms is less desirable than modified release drug delivery systems.

This fact coupled with the intrinsic inability of conventional dosage forms to achieve spatial placement, is a compelling motive for investigation of modified release drug delivery.

1.1.2 Nomenclature to describe modified release dosage forms

A number of terms and phrases have been used to describe the oral dosage forms that portray modified release properties; which include delayed release, repeated action, prolonged release, extended release, controlled release and sustained release. Each drug delivery system is aimed at eliminating the cyclical changes in plasma drug concentration seen after administration of conventional delivery systems [7].

Modified release dosage forms are designed to provide quick achievement of a drug plasma level that remains constant (i.e. controlled release) at a value within the therapeutic range of a drug for a significant temporal period of time or achievement of a plasma concentration of a drug that delivers at a slow rate (i.e. sustained release) that stays within the therapeutic range for a longer period of time. Based on the assumption that a drug, which is to be incorporated into a modified release dosage form, confers upon the body the characteristics of a one-compartment open model, then the basic kinetic design of such a product may be assumed to contain two portions, one that provides the initial priming/loading dose, and one that provides the maintenance or sustained dose. To ensure that the therapeutic concentration of the
drug in the body remains constant, two conditions must be fulfilled, namely 1) the zero order rate of drug release must determine the absorption rate of the drug, and 2) the rate at which the drug is released from the maintenance dose (and subsequently the absorption rate) should be equal to the rate of drug elimination at the required steady-state concentration. A list of important terms that describe different modified release dosage forms are defined below [8].

**Modified release dosage forms**: defined by the USP23 (1995) as those dosage forms whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms.

**Delayed release** indicates that the drug is not being released immediately after administration but at a later time.

**Repeat action** indicates that an individual dose is released fairly soon after administration, and second or third doses are subsequently released at intermittent intervals.

**Prolonged release** indicates that the drug is provided for absorption over a longer period of time than from a conventional dosage form. However, there is an implication that onset is delayed because of an overall slower release rate from the dosage form.

**Extended release** slow release of the drug so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 and 12 hr).

**Controlled release** The drugs are released at a constant (zero order) rate and provide plasma drug concentration that remains invariant with time.
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**Sustained release:** the pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration. The onset of its pharmacological action is often delayed, and the duration of its therapeutic effect is sustained.

1.1.3 Sustained drug delivery

A new development namely, sustained drug release dosage forms, has evolved from the need for a prolonged drug effect, a better control of drug administration and the reduction of side-effects. In general, the goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of drug for an extended period. This is usually accomplished by attempting to obtain zero-order release from dosage form.

Fig. 1.1.3 represents a typical drug kinetic pattern for immediate release, controlled release (zero order) and sustained release dosage forms.
In conventional drug delivery systems, the drug concentration in the blood rises when the drug is being administered, then peaks and declines almost to zero. Each individual drug has a maximum safe concentration and a minimum effective concentration. Fluctuations in plasma concentration may mean that drug levels may swing too high leading to toxic side-effects; alternatively drug may fall too low leading to a lack of efficacy. Furthermore, the plasma drug concentration in a patient at a particular time depends on the compliance with the prescribed dosage interval.

Sustained drug delivery systems maintain the drug effect in desired therapeutic range with just a single dose, simulating an intravenous infusion of a drug, localizing drug delivery to a particular body compartment, improving tolerability and reducing the need to follow-up pharmaceutical care (i.e. improving patient comfort and
compliance). These dosage forms could also preserve medications that are rapidly
destroyed by the body [10, 11].

1.1.3.1 Principle of sustained drug delivery [9]

The conventional dosage forms release their active ingredients into an absorption pool
immediately. The absorption pool represents a solution of the drug at the site of
absorption. The terms Kr, Ka and Ke are first order rate constants for drug release, absorption and overall elimination respectively. Immediate release of drug from conventional dosage form implies that Kr >>> Ka. Alternatively speaking the absorption of drug across a biological membrane is the rate limiting step. For non-immediate release dosage forms, Kr <<< Ka, i.e., the release of drug from the dosage form is the rate-limiting step.

The main objective in designing a sustained release system is to deliver the drug at a rate necessary to achieve and maintain a constant blood level. This rate should be analogous to that achieved by continuous i.v. infusion where the drug is provided to the patient at a constant rate 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. The release of a drug from the dosage form should follow zero order kinetics, as shown by the equation 1,

\[ K_0 r = \text{Rate In} = \text{Rate Out} = Ke \times Cd \times Vd \]  

Where, \( K_0 r \) = Zero order rate constant for drug release (amount per time),
\( Ke \) = First order rate constant for overall drug elimination (time\(^{-1}\)),
\( Cd \) = Desired drug level in the body (amount per volume),
\( Vd \) = Volume space in which the drug is distributed (liters).
The values of $K_r$, $C_d$ and $V_d$ needed to calculate $K_0r$ are obtained from appropriately designed single dose pharmacokinetic study. It is important to recognize that while zero order release may be desired theoretically; non-zero order release may be equivalent clinically to constant release in many cases.

1.1.3.2 Advantages of sustained drug therapy [2]

1. Avoid patient compliance problems.
2. Employ less total drug,
   a) Minimize or eliminate local side effects
   b) Minimize or eliminate systemic side effects
   c) Obtain less potentiation or reduction in drug activity with chronic use
   d) Minimize drug accumulation with chronic dosing
3. Improve efficiency in treatment,
   a) Cure or control condition more promptly
   b) Improve control of condition i.e. reduce fluctuation in drug level
   c) Improve bioavailability of some drugs
   d) Make use of special effects, e.g. sustained release aspirin for relief of arthritis in morning by dosing before bedtime

4. Economy

Although the initial unit cost of most sustained release drug delivery systems is usually greater than that of conventional drug delivery systems, but the average cost of treatment over an extended time period may be less. Economy may result from a decrease in nursing time, reduction in hospitalization, less lost work time, etc. The most important reason for sustained drug therapy is improved efficiency in the treatment i.e., optimized therapy.
1.1.3.3 Disadvantages of sustained drug therapy

1. Administration of sustain release medication does not permit the prompt termination of therapy.

2. The physician has less flexibility in adjusting the dosage regimens. This is fixed by the dosage form design.

3. Sustained release forms are designed for normal population i.e., on the basis of average drug biologic half-life. Problems may be observed in diseased conditions where drugs disposition is altered, if the liver and kidney functions are impaired.

4. Economic factors must also be assessed, since more costly processes and equipments are involved in manufacturing of any sustained release dosage forms.

1.1.4 Release pattern of drug from polymer matrices

Recently, several technical advancements have been made in the development of new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity, and/or targeting the delivery of drug to a tissue. Although these advancements have led to the development of several novels drug delivery systems that could revolutionaries the method of medication and provide a number of therapeutic benefits. It also creates some confusion in the terminology between ‘controlled release’ and ‘sustained release’. Unfortunately these terms have been often used interchangeably in the scientific literature and technical presentations over the years.
1.1.4.1 Methods for preparing sustained release oral dosage form

The most acceptable technologies used to obtain sustained release oral products are as follows: [12]

1. Release from slow eroding solid matrices,
2. Release from solid hydrophilic gel matrices,
3. Release from porous inert solid matrices,
4. Release from coated granules disintegrating at a controlled rate,
5. Release from granules coated with diffusion controlling membrane,
6. Release from ion exchange resin complexes, and
7. Release by reducing the solubility of drugs.

1.1.5 Formulation of modified release dosage forms

The basic principle that governs all modified release dosage forms is drug diffusion that occurs from a region of high concentration to a region of low concentration. This concentration difference is the driving force for drug diffusion out of the system. The inside of the system should have lower water content initially than the surrounding medium to control the diffusion of a drug effectively. 8

Different methods have been employed to provide modified drug release, which include modifications to the physical and chemical properties of the drug or changes to the dosage form as indicated in Fig. 1.1.4
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Figure 1.1.4 Summarized representation of the methods to modify drug release

[7, 8]

1.1.5.1 Methods to modify drug release by drug modification

These methods take advantage of the changes in the physicochemical properties of drug moieties caused by complex formation, drug adsorbate preparations and prodrug synthesis. These modifications are possible only with drug moieties containing appropriate functional groups. This approach is independent of the dosage form design. 

Fig. 1.1.5 shows the mechanisms of sustained release based on drug modification. In the case of drug complexes the effective release rate of the drug is a function of two processes, including the rate of dissolution and breakdown of the complex in a solution. If the rate of dissolution is greater than the rate of dissociation, a zero-order release pattern might be achieved. In this case, the concentration of the complex is
maintained at its saturation point if the solubility of the complex is sufficiently low so that excess solid complex is present during the onset of the maintenance time. If the rate of dissociation is greater than the rate of dissolution, the dissolution of the complex will be the rate-determining step [7].

Figure 1.1.5 Mechanisms of sustained modification [7].

Another approach for drug modification is through the formulation of a prodrug. This can be achieved through designing a bio-reversible derivative (prodrug) that can afford an increased or selective transport of the drug to the site of action (e.g., levodopa as prodrug for the central nervous system anti-parkinsonism agent dopamine) or by designing a derivative that goes everywhere in the body but undergoes bio-activation only on the target. The solubility, specific absorption rate and elimination rate constant of an effective prodrug should be significantly lower than that of the parent drug. In drug adsorbates, drug availability is determined only
by the rate of dissociation and by the access of the adsorbate surface to water as well as the effective surface area of the adsorbate [7].

1.1.5.2 Methods to modify drug release by dosage form modification

The most modified release dosage forms of this class employ either an embedded matrix or a physical barrier principle to provide slow release of the maintenance dose. The techniques used to build this matrix or barrier into the dosage form include the monolithic or matrix systems, the reservoir or membrane controlled systems, the osmotic pump systems, coated beads and micro encapsulation [7, 8, 13].

1.1.5.2.1 Monolithic or matrix systems

These systems can be divided into two groups: (1) those with drug particles dispersed in a soluble matrix, with drug becoming available as the matrix dissolves or swells and dissolves (hydrophilic colloid matrices); and (2) those with drug particles dispersed in an insoluble matrix, with drug becoming available as a solvent enters the matrix and dissolves the particles (lipid matrices and insoluble polymer matrices)

Drugs dispersed in a soluble matrix rely on slow dissolution of the matrix to provide sustained release. Excipients used to provide a soluble matrix often are those used to make soluble film coatings. Alternatively, slowly dissolving fats and waxes can be used. Synthetic polymers, such as poly orthoesters and poly anhydrides, have also been used. These polymers undergo surface erosion with little or no bulk erosion. If the matrix is presented with conventional tablet geometry, then on contact with dissolution media the surface area of the matrix decreases with time, with a concomitant decrease in drug release.

Drug particles may be incorporated into an insoluble polymer matrix. Drug release from these matrices follows penetration of fluid into the formulation, followed by dissolution of the drug particles and diffusion of the solute through fluid-filled pores.
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This type of delivery system would not be suitable for the release of compounds that are insoluble or those compounds that have low aqueous solubility. Excipients used in the preparation of insoluble polymers include hydrophobic polymers such as polyvinyl acetate, ethyl cellulose and some waxes. At this point each of the three main types of monolithic/matrix systems will be discussed.

1.1.5.2.1.1 Lipid matrix systems

Wax matrices prepared by direct compression; hot-melt granulation or roller compression; have their active agent contained in a hydrophobic substance that remains intact during drug release. The release of the drug depends on an aqueous medium dissolving the channeling agent, which leaches out of the matrix forming capillary pores. The active ingredient then dissolves in the aqueous medium and diffuses out of the matrix, by way of the water-filled capillaries. A typical formulation consists of an active drug, a wax matrix former (hydrophobic material that are solids at room temperature and do not melt at body temperature, e.g., hydrogenated vegetable oils, cottonseed oils, soya oils, microcrystalline wax and carnauba wax), a channeling agent (soluble in the GIT, in water and leaches out of the formulation leaving tortuous capillaries through which the dissolved drug may diffuse in order to be released, e.g., sodium chloride and sugars), solubiliser and pH modifier, an anti-adherent/glidant and a lubricant.

1.1.5.2.1.2 Insoluble polymer matrix systems

Drugs are embedded in an inert polymer, which is not soluble in the gastrointestinal fluid. Drug release has been compared to the leaching from a sponge. The release rate depends on drug molecules in aqueous solution diffusing through a network of capillaries formed between compact polymer particles. The factors influencing drug release rate from insoluble polymer matrix systems are-
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- Pore structure - pore forming salts and compression force,
- Excipients - wettability changed by the soluble and insoluble components,
- Particle size of polymer component - influences the surface area exposed to the medium.

There are three primary mechanisms by which active agents can be released from a matrix delivery system, which involve diffusion, degradation, and swelling followed by diffusion. Any or all of these mechanisms may occur in a given drug release system. Diffusion occurs when a drug or other active agent passes through the polymer that forms the modified-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. The particle size of the insoluble matrix components influences the release rate, larger particles leading to an increase in release rate. This is attributed to these coarser particles producing matrices with a more open pore structure. An increase in drug loading tends to enhance release rate, but the relationship between the two is not clearly defined. One possible explanation may be a decrease in the tortuosity of the matrix.

An insoluble polymer and an active agent have been mixed to form a homogeneous system, also referred as a matrix diffusion system as shown in Fig. 1.1.6. 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 1.1.6 Drug delivery from an insoluble polymer matrix diffusion system.

1.1.5.2.1.3 Hydrophilic colloid matrix systems

A hydrophilic matrix, controlled release system is a dynamic one involving polymer wetting, polymer hydration, gel formation, swelling and polymer dissolution. At the same time, other soluble excipients or drugs will also wet, dissolve, and diffuse out of the matrix while insoluble materials will be held in place until the surrounding polymer/excipient/drug complex erodes or dissolves away.

The mechanisms by which drug release is controlled in matrix tablets are dependent on many variables. The main principle is that the water-soluble polymer which present throughout the tablet, hydrates on the outer tablet surface to form a gel layer (Fig. 1.1.7). Throughout the life of the ingested tablet, the rate of drug release is determined by diffusion (if soluble) through the gel and by the rate of tablet erosion. With soluble drugs, the primary drug release mechanism is by diffusion through the gel layer and with insoluble drugs, the primary drug release mechanism is by surface
erosion. A fast rate of hydration followed by quick gelation and polymer/polymer coalescing is necessary for a rate-controlling polymer to form a protective gelatinous layer around the matrix. This prevents the tablet from immediate disintegration, resulting in premature drug release. Fast polymer hydration and gel layer formation are critical when formulating with water-soluble drugs and water-soluble excipient.

![Diagram of drug release from a matrix tablet](image)

**Figure 1.1.7 Drug release from a matrix tablet [14].**

These swellable-soluble matrices are hydrogels that swell on hydration. The systems are capable of swelling followed by gel formation, erosion and dissolution in aqueous media. Their behavior is in contrast to a true hydrogel, which swells on hydration but does not dissolve. Drug particles are dispersed in an insoluble matrix and the drug becomes available as the solvent enters the matrix and dissolves the drug particles. This is enhanced by the swelling, which is followed by gel formation, erosion of the matrix system and the dissolution of the drug. Hydrophilic polymer matrix systems comprise a mixture of the drug, the hydrophilic colloid, release modifiers and lubricant/glidant. Diffusion of the drug through the hydrated matrix is the rate limiting step in drug release. The tortuosity of the diffusion path and the ‘micro-viscosity’ and
interactions within the interstitial continuum govern the diffusion of the drug through the hydrated gel layer and hence, the release of the drug.

Two common types of hydrophilic matrix systems are the true gels which are cross-linked polymeric structures formed by chemical bonds (covalent) or physical bonds (helix formation based on hydrogen bonds or ionic interactions), for which gelatin is an excellent polymeric example, and the viscous matrices which are simple entanglements of adjacent polymer chains, e.g., HPMC and alginates.

**Table 1.1.1 Comparison of different types of hydrophilic colloid matrix systems** [8].

<table>
<thead>
<tr>
<th>True gel matrices</th>
<th>Viscous matrices</th>
</tr>
</thead>
<tbody>
<tr>
<td>• The diffusion pathway is via the continuous phase in the interstices of the gel</td>
<td>• The diffusion pathway is via the continuous phase trapped between the adjacent polymeric chains</td>
</tr>
<tr>
<td>• The cross-links are more or less 'fixed' after the gel has formed</td>
<td>• There are no 'fixed' cross-links</td>
</tr>
<tr>
<td>• The bulk viscosity of the gel is derived from the structure of the cross-linked polymeric chains with a contribution from the continuous phase</td>
<td>• The bulk viscosity is related to the enlargement of adjacent polymer chains which are free to move within the continuous phase</td>
</tr>
<tr>
<td>• Bulk viscosity generally does not correlate with diffusion</td>
<td>• Bulk viscosity correlates with diffusion</td>
</tr>
<tr>
<td>• Diffusion in the gel correlates with 'microviscosity'</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.1.1 compares the different types of hydrophilic colloid matrix systems, which are the true gel matrix system and the viscous matrix system. The two are more like extreme opposites of each other in terms of their cross-linked chain structure, viscosity and the ways they release drug substances.
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1.1.6 Polymers in drug delivery

One of the most remarkable and useful features of a polymer's swelling ability manifests itself when that swelling can be triggered by a change in the environment surrounding the delivery system. Ranges of materials have been employed to control the release of drugs and other active agents. The earliest of these polymers were originally intended for non-biological uses and were selected because of their desirable physical properties. To be successfully used in controlled drug delivery formulations, a material must be chemically inert and free of leachable impurities. It must also have an appropriate physical structure, with minimal undesired aging and be readily processable. However, in recent years additional polymers designed primarily for medical applications have entered the arena of controlled release. Many of these materials are designed to degrade within the body [8].

Hydrophilic matrices are an interesting option when developing an oral sustained release formulation. They can be used for controlled release of both water soluble and water insoluble drugs. The release behavior of drugs varies with the nature of the matrix and its complex interaction of swelling, diffusion and erosion process [15-19].

1.1.6.1 Classification of hydrophilic polymers

The hydrophilic polymers can be arranged into three broad groups: [20]

1. **Non-cellulose Natural or Semisynthetic Polymers**: These are products of vegetable origin and are generally used for pharmaceutical purpose. Agar [21], alginates [22-24], chitosan [25-28], xanthan gum [29], guar gum [29-32], carrageenan [33, 34], starches [35-39] etc., are commonly used polymers.

2. **Polymer of Acrylic acid**: These are arranged in the carbomer group and commercialized under the brand name of Carbopol [40]. The major
disadvantage of this type of polymers is its pH dependent gelling characteristics [41-44].

3. **Cellulose Ethers:** This group is semi-synthetic cellulose derivatives is the most widely used group of polymers. Non-ionic polymers such as HPMC of different viscosity grades are widely used [45-47], Methylcellulose [48], in contrast, has not proved especially useful in this field. In the last few years a number of interesting applications of the ionic sodium CMC have been found [48-52].

1.1.6.2 **Advantages of hydrophilic matrix tablets** [3, 53-59]

1. Proper control of the manufacturing process, reproducible release profiles are possible.

2. Though the structure makes the immediate release of a small amount of active principle, there is no risk of 'dose dumping'.

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

4. The manufacturing processes are notably straight forward. The usual route of formulating tablets is done via direct compression or by wet granulation.

5. Large variety of non-expensive gelling agents is approved for oral use by the competent official organizations.

6. Comparatively simple concept.

7. Excipients are generally economic and are usually GRAS (Generally Regarded As Safe).

8. Capable of sustaining high drug loadings.

9. Erodible, so reducing the possibility of 'ghost' matrices.

10. Well established technology.
1.1.6.3 Disadvantages of hydrophilic matrix tablets

1. 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 shear the hydrated polymer gel layer to cause dose dumping or it may block the pores of the matrix and inhibit the drug release rate.

2. Release of the drug is dependent on two diffusion processes.

   [a] Penetration of water through the hydrated matrix into the non-hydrated core, and

   [b] Diffusion of dissolved drug through the hydrated matrix.

3. Required batch-to-batch consistency in the matrix forming materials, other components and process parameters.

4. Need optimal rate-controlling polymers for different actives.

1.1.7 Matrix diffusion-controlled drug delivery systems [60, 61]

In this type of sustained release drug delivery systems, the drug reservoir results from the homogeneous dispersion of drug particles in either a lipophilic or a hydrophilic polymer matrix. Fig. 1.1.8 shows the top of a swellable matrix tablet during drug release showing the three fronts.

**The swelling front**, the boundary between the glassy polymer and its rubbery phase.

**The diffusion front**, the boundary between the solid as yet undissolved drug and the dissolved drug in gel layer, and

**The erosion front**, the boundary between the matrix and the dissolution medium.

The mechanisms of drug release from swellable matrix are diffusion of drug through the gel layer and drug transport due to relaxation of the polymer. The rate of diffusion through the gel layer depends on drug dissolution and matrix erosion, both evidently...
affecting the drug concentration gradient in gel layer. Drug release from swellable matrix tablet is strictly linked to gel layer dynamics, also where the solubility of the drug is so low that the possibility exists for it to be released as solid particles from the dissolving layer of gel.

Figure 1.1.8 Picture of the top of a swellable matrix tablet during drug release showing the three fronts [18].

The drug dispersion in the polymer matrix is accomplished either by blending a dose of finely ground drug particles with a viscous liquid polymer or a semisolid polymer, followed by cross linking of polymer chains or mixing drug particles with a melted polymer. The resultant drug-polymer dispersion is then extruded to form drug delivery devices of various shapes and sizes designed for specific application. It can also be fabricated by dissolving the drug and the polymer in a common solvent,
follows by solvent evaporation in a mold at an elevated temperature and/or under a vacuum.

The rate of drug release from this matrix diffusion controlled drug delivery systems is time dependent and defined in equation 2,

\[
\frac{dq}{dt} = \left( \frac{A \times Cr \times Dp}{2t} \right)^{1/2}
\]

Where, A is the loading dose initially dispersed in the polymer matrix, Cr is the drug solubility in the polymer, which is also the drug reservoir concentration in the polymer matrix, and Dp is the diffusivity of the drug molecule in the polymer matrix.

The following equation is obtained on integration of equation 2,

\[
\frac{Q}{t^{1/2}} = \left( \frac{2A \times Cr \times Dp}{2t} \right)^{1/2}
\]

Where, Q defines the flux of drug release at steady state from matrix diffusion controlled drug delivery system.

Hydrophilic matrix dosage forms essentially consist of a compressed blend of hydrophilic polymer and drug. According to the generally accepted mechanism (Fig.1.1.8), the drug release from hydrophilic matrix dosage forms starts when the tablet comes in contact with GI fluid. The surface of the tablet hydrates to release exposed drug and at the same time form a viscous polymer mucilage or gel. This gel fills the interstices within the tablet retarding further ingress of liquid.
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