Abstract

Controlled release products are designed to maintain constant therapeutic plasma concentration of the drug within the therapeutic range of the drug over a prolonged period and offer minimum side effects. This can be achieved using a variety of delivery systems. These products are designed to reduce the frequency of dosing by modifying the rate of drug absorption. The frequency of administration or the dosing interval of any drug depends upon its half-life or mean residence time (MRT). Generally, controlled release products administered by any route are designed such that the rate of drug absorption should be equal to the rate of drug elimination. There are different types of controlled drug delivery systems. The development or selection of system further depend upon the physicochemical and pharmacological properties of the active pharmaceutical ingredient. One of the least complicated approaches to the manufacture of controlled release dosage forms involves the direct compression of blend of drug, retardant material, and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Matrix tablets is a promising approach for the establishment of extended release drug therapy as tablets offer the lowest cost approach to sustained and controlled release.

Keywords: controlled release, plasma concentration, frequency of dosing, Matrix tablets.

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INTRODUCTION

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively complete systemic drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentration decline according to the drug’s pharmacokinetic profile [1]. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage from that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms. In recent years, various modified-release drug products have been developed to control the release rate of the drug and / (or) the time for drug release [2].

Modified Drug Delivery System

The term Modified-release drug product is used to describe products that alter the timing and/ (or) the rate of release of the drug substance. A modified dosage form is defined “as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized [3].”

Types of Modified Release Drug Products

Several types of modified –release drug products are recognized [4].

1) Extended-Release Drug Products: A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long acting drug products.

2) Delayed-Release Drug Products: A dosage form that releases a discrete portion or portions of drug at a time (or) at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

3) Targeted-Release Drug Products: A dosage forms that release drug at or near the intended physiologic site of action. Targeted-release dosage forms may either immediate (or) extended- release characteristics.
The term controlled-release drug product was previously used to describe various types of oral extended-release-rate dosage forms, including sustained-release, sustained action, long-action, slow-release, and programmed drug delivery.

**Conventional Drug Delivery System [5]**

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid (or) immediate absorption. As can be seen in the graph (Figure 1), administration of the conventional dosage form by extra-vascular route does not maintain the drug level in blood for an extended period of time. The short duration of action is due to the inability of conventional dosage form to control temporal delivery.

![Fig.1: A hypothetical plasma concentration-time profiles from conventional multiple dosing and single doses of sustained and controlled delivery formulations](image)

The conventional dosage forms like solutions, suspension, capsules, tablets and suppository etc. have some limitations such as:

- Drugs with short half-life require frequent administration, which increases chances of missing the dose of drug leading to poor patient compliance.
- A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult. The unavoidable fluctuations in the drug concentration may lead to under medication (or) overmedication as steady state concentration values fall (or) rise beyond the therapeutic range.
- The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overdosing occurs.
- In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system.
that could revolutionize method of medication and provide a number of therapeutic benefits [7].

**Controlled Release Drug Delivery Systems (CRDDS)**

More precisely, controlled delivery can be defined as [8]

- Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
- Localized drug action by spatial placement of a controlled release system adjacent to (or) in the diseased tissue.
- Targeted drug action by using carriers (or) chemical derivatives to deliver drug to a particular target cell type.
- Provide a physiologically / therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/therapeutic needs of the body.

A controlled drug delivery system is usually designed to deliver the drug at a particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. This predetermined rate of drug release is based on the desired therapeutic concentration and the drug’s pharmacokinetics.

**Advantages of Controlled Release Drug Delivery Systems [9,10]**

- Overcome patient compliance problems.
- Employ less total drug
  - Minimize (or) eliminate local side effects
  - Minimize (or) eliminate systemic side effects
  - Obtain less potentiation (or) reduction in drug activity with chronic use
  - Minimize drug accumulation with chronic dosing
- Improves efficiency in treatment
  - Cures (or) controls condition more promptly.
  - Improves control of condition i.e., reduced fluctuations in drug level.
  - Improves bioavailability of some drugs.
  - Make use of special effects, e.g., sustained-release aspirin for monitoring relief of arthritis by dosing before bed time.
- Economy i.e., reduction in health care costs. The average cost of treatment over an extended time period may be less, with lesser frequency of dosing, enhanced therapeutic benefits and reduced side effects. The time required for health care personnel to dispense and administer the drug and monitor patient is also reduced.

**Disadvantages of Controlled Release Drug Delivery Systems** [9,10]
- Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.
- Poor *In vitro – In vivo* correlation.
- Retrieval of drug is difficult in case of toxicity, poisoning (or) hypersensitivity reactions.
- Reduced potential for dose adjustment of drugs normally administered in varying strenght

**Oral Controlled Drug Delivery Systems** [11,12]

Oral controlled release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local (or) systemic action [11].

**Classification of Oral Controlled Release Systems** [12,13]

Among all routes of administration, the oral route has been most popular and successful. Oral controlled delivery systems can be broadly divided into following categories, based on their mechanism of drug release:

1. Dissolution- Controlled release
   a. Encapsulation dissolution control
   b. Matrix dissolution control
2. Diffusion-Controlled release
   a. Reservoir devices
   b. Matrix devices
3. Combination of Dissolution and Diffusion systems.
4. Ion Exchange System.
5. Osmotic Pressure System.
7. Altered Density System.

**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) subclass of diffusional systems are recognized.

- **Reservoir devices Diffusion control and;**
- **Matrix devices.**

It is very common for the diffusion-controlled devices to exhibit a non-zero order release rate to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds.

![Diagram of Diffusion Controlled Devices](image)

**Fig.2: Diffusion of Controlled Devices (a) Rigid Matrix (b) Swellable Matrix**

**Reservoir Devices Diffusion Control**

In this system water insoluble polymeric material encases a core of drug. Drug will partition into membrane and exchange with the fluid surrounding the particles (or) tablets (or) capsules.

![Diagram of Reservoir System](image)

**Fig. 3: Schematic Representation of Diffusion Reservoir System**
The release rate is given by equation:

\[
\frac{Dm}{dt} = A.D.K.\Delta c/L
\]  
............ (1.1)

Where,

A is the Area

D is the Diffusional Coefficient

K is the partition coefficient of the drug between the membrane and drug core.

L is the diffusional path length.

\(\Delta C\) is the concentration difference across the membrane.

An important parameter in the above equation is the partition coefficient, which is defined as the concentration, of the drug in the membrane over the concentration of the drug in the core. If the partition coefficient is high, the core will be depleted of the drug in a short time so that zero order release will be observed only over a short segment of time course of the drug.

To obtain a constant drug release rate all the terms in the right hand side of the above equation must be held constant. Methods to develop reservoir type devices include press coating, air suspension coating techniques. Micro-encapsulation process is a commonly used to coat the drug particles incorporated.

**Matrix Diffusion Control**

In this type a solid drug is dispersed in an insoluble matrix and the rate of release of drug is independent on the rate of diffusion and not on the rate of solid dissolution.

Higuchi has derived the equation describing drug release from this system which is given below,

\[
Q = \left[ \frac{(DE/T) (2A-EC_s) C_{s,t}}{C_s} \right] 
\]  
............ (1.2)

Fig.4: Schematic Representation of Diffusion Matrix System.
Where,

Q is weight in grams of drug released per unit area at time ‘t’.

D is diffusion coefficient of drug on release medium.

E is the porosity of matrix.

C_s is the solubility of drug in the release medium.

T is the tortuosity of matrix.

A is the concentration of drug in the tablet expressed as gm/mL.

**Dissolution Controlled Systems**

**Matrix Dissolution Controlled System**

This approach is achieved by formulating the drug into matrix systems using hydrophilic swellable polymers.

Dissolution is controlled by

- Altering porosity of tablet.
- Decreasing in wetteability.
- Dissolving at slower rate.

Drug release is determined by dissolving by dissolution rate of polymer. Examples of such matrix dissolution system is Dimetane extencaps, aqueous dispersions, congealing, spherical agglomeration etc. can be used.

Fig.5: Schematic representation of Matrix Dissolution System

1) **Reservoir (or) Encapsulation Dissolution Control**

- It is also called as Coating dissolution controlled systems.
- It is achieved by encapsulating the drug within slowly soluble polymeric membranes in the form of tablets (or) capsules.
- Dissolution rate of coat depends upon stability and thickness of coating.
- It is useful in masking colour, odour, taste, minimizing GI irritation.

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Examples of Reservoir dissolution control are Ornade Spansules, Particles, seeds (or) granules can be coated by technique such as microencapsulation.

![Fig.6: Schematic representation of Encapsulation Dissolution Control](image)

**Diffusion and Dissolution Controlled System**

In a bio-erodible matrix, the drug is homogenously dispersed in a matrix and it is released either by swelling controlled mechanism (or) by hydrolysis (or) by enzymatic attack. As a further complication these systems can combine diffusion and dissolution of both drug and the matrix material. Drugs not only can diffuse out of dosage form, as with some previously described matrix systems, but also the matrix itself undergoes a dissolution process. The complexity of the systems arises from the fact that as the polymer dissolves the diffusional path length for 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.

![Fig.7: Diffusion and Dissolution Controlled Systems](image)
Ion Exchange Resin

It is based on the drug resin complex formation when an ionic solution is kept in contact with ionic resins. The drug from these complexes gets exchanged in gastrointestinal tract and released with excess of sodium and chloride ions present in gastrointestinal tract.

Osmotic Pressure System

It is characterized by drug surrounded by semi permeable membrane and release governed by osmotic pressure.

Advantages:

- Zero order release rates are obtainable.
- Pre-formulation is not required for different drugs.
- Release of drug is independent of the environment of the system.

Disadvantages:

- System can be much more expensive than conventional counterparts.
- Quality control is more extensive than most conventional tablets.

pH – Independent System

A buffered controlled release formulation is prepared by mixing a basic (or) acidic drug with one (or) more buffering agents, granulating with appropriate pharmaceutical excipient and coating with GI fluid permeable film forming polymer. When GI fluids permeate through the membrane the buffering agent adjusts the fluid inside to suitable constant pH thereby a constant rate of drug release.

Altered Density System

Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract.

- High-density approach.
- Low-density approach.

Types of Extended –Release Products [14]

General approaches for manufacturing an extended-release drug product include the use of a matrix structure in which the drug is suspended (or) dissolved, the use of a rate - controlling
membrane through which the drug diffuses, (or) a combination of both. Among the many types of commercial preparations available, none works by a single drug-release mechanism. Most extended-release products release drug by a combination of processes involving dissolution, permeation, and diffusion. The single most important factor is water permeation, without which none of the product release mechanisms would operate. Controlling the rate of water influx into the product generally dictates the rate at which the drug dissolves. Once the drug is dissolved, the rate of drug diffusion may be further controlled to a desirable rate.

Table 1: Examples of Oral Controlled Extended Release Products

<table>
<thead>
<tr>
<th>Type</th>
<th>Trade Name</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erosion tablet</td>
<td>Erosion tablet</td>
<td>Theophylline</td>
</tr>
<tr>
<td></td>
<td>Constant-T</td>
<td>Theophylline</td>
</tr>
<tr>
<td></td>
<td>Tenuate Dospan</td>
<td>Diethylpropion HCl dispersed in hydrophilic matrix</td>
</tr>
<tr>
<td></td>
<td>Tedral SA</td>
<td>Combination product with a slow-erosion component (theophylline, ephedrine HCl) and an initial-release component theophylline, ephedrine HCl, phenobarbital</td>
</tr>
<tr>
<td>Waxy matrix tablet</td>
<td>Kaon Cl</td>
<td>Slow release of potassium chloride to reduce GI irritation</td>
</tr>
<tr>
<td>Coated pellets in capsule</td>
<td>Ornade spansule</td>
<td>Combination phenylpropanolamine HCl and chlorpheniramine with initial- and extended-release component</td>
</tr>
<tr>
<td>Pellets in tablet</td>
<td>Theo-Dur</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Leaching</td>
<td>Ferro-Gradumet (Abbott)</td>
<td>Ferrous sulfate in a porous plastic matrix that is excreted in the stool; slow release of iron decreases GI irritation</td>
</tr>
<tr>
<td></td>
<td>Desoxyn gradumet tablet (Abbott)</td>
<td>Methamphetamine methylacrylate methylmethacrylate copolymer, povidone, magnesium stearate; the plastic matrix is porous</td>
</tr>
<tr>
<td>Coated Ion Exchange</td>
<td>Tussionex</td>
<td>Cation ion-exchange resin complex of hydrocodone and phenyltoloxamine</td>
</tr>
</tbody>
</table>

Factors Influencing the Design and Performance of Oral Controlled Release Drug Products

The types of delivery systems and route of administration of the drug presented in sustained drug delivery system may depend upon two properties [2, 15, 16]. They are
- Physicochemical Properties of drugs
- Biological Factors

PHYSICOCHEMICAL PROPERTIES OF DRUGS

Dose size

For orally administered systems, there is an upper limit to bulk size of the dose to be administrated. In general a single dose of 0.5 to 1gm is considered maximum [17]

Ionization, Dissociation Constant (P\text{ka}), & 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 the P\text{ka} the compound and its absorptive environment. For many compounds' the site of absorption will also be the area in which the rug is least soluble. For conventional dosage forms the drug can be generally fully dissolve in the stomach and then absorbed in the alkaline pH of the intestine. For sustained release formulations 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 controlled, since their release over time course of a dosage form in the GIT will be limited by dissolution of the drug. The lower limit for solubility of a drug to be formulated in a sustained release system has been reported to be 0.1mg/ml \cite{18}. Thus for slightly soluble drugs, diffusional systems will be poor choice, since the concentration in solution will be low. For example Tetracycline has maximum solubility in the stomach and least solubility in the intestine where it is maximally absorbed. Other examples of drugs whose incorporation into sustained release systems are limited because of their poor aqueous solubility and slow dissolution rate are Digoxin, warfarrin, Griseofulvin and Salicylamide. Very soluble drugs are also good candidates for the sustained release dosage forms.

Partition Coefficient

The compounds with a relatively high partition coefficient are predominantly lipid soluble and easily penetrate membranes resulting high bioavailability. Compounds with very low partition coefficient will have difficulty in penetrating membranes resulting poor bioavailability. Furthermore partitioning effects apply equally to diffusion through polymer membranes.
Drug Stability

The drugs, which are unstable in stomach, can be placed in a slowly soluble form and their release delayed until they reach the small intestine. However, such a strategy would be detrimental for drugs that either are unstable in the small intestine (or) undergo extensive gut wall metabolism, as pointed out in the decrease bioavailability of some anticholinergic drugs from controlled/sustained release formulation. In general the drugs, which are unstable in GIT environment poor candidates for oral sustained release forms.

Protein Binding

It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are mostly recirculated and not eliminated. Drug protein binding can serve as depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs.

Molecular Size and Diffusivity

With large molecular size are poor candidate for oral controlled release. Where it is 1st time drug delivery system because the ability of the drug to diffuse polymeric membrane is a function of its diffusivity. Diffusivity depends upon size, shape of the cavities of the membrane. The examples of drugs which are difficult to control release rate of medicament from dosage from are proteins.

BIOLOGICAL PROPERTIES OF DRUGS

Absorption

The characteristics of absorption of a drug can greatly affect its suitability as a sustained release product. Drugs which are absorbed by specialized transport process (carrier mediated) and drug absorption at special sites of the gastrointestinal tract (Absorption Window) are poor candidates for sustained release products. The compounds with lower absorption rate constants are poor candidates for modified drug delivery systems.

Distribution

The distribution of drugs in tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate
limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition.

**Biological Half-Life [13]**

Therapeutic compounds with half-life less than 8hrs are excellent candidates for sustained release preparations. Drugs with very short half-life (less than 2hrs) will require excessively large amounts of drug in such dosage unit to maintain controlled effects. Thus forcing the dosage form itself to become too large to be administered. Compounds with relatively long half-lives, generally greater than 8hrs are not used in the sustained release dosage forms, since their effect is already sustained and also GI transit time is 8-12hrs. So the drugs, which have long half-life and short half-life, are poor candidates for sustained release dosage forms. Some examples of drug with half-life of less than 2 hours are ampicillin, cephalexin, cloxacillin, furosemide, levodopa, penicillin G and propylthiouracil. Examples of those with half-lives of greater than 8hours are dicumarol, diazepam, digitoxin, digoxin, guanethidine, phenytoin and warfarin.

**Metabolism [19]**

The metabolic conversion of a drug to another chemical form usually can be considered in the design of a sustained-release system for that drug. As long as the location, rate and extent of metabolism are known and the rate constant(s) for the process (es) are not too large, successful sustained-release products can be developed. There are two factors associated with the metabolism of some drugs; however that present problems of their use in sustained-release systems.

- One is the ability of the drug to induce (or) inhibit enzyme synthesis; this may result in a fluctuating drug blood level with chronic dosing.
- The other is a fluctuating drug blood level due to intestinal (or other tissues) metabolism (or) through a hepatic first-pass effect.

Examples of drugs that are subject to intestinal metabolism upon oral dosing are hydralazine, salicylamide, nitroglycerine, isoproterenol, chlorpromazine and levodopa. Examples of drugs that undergo extensive first-pass hepatic metabolism are propoxyphene, nortriptyline, phenacetine, propane and lidocaine. 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. The drugs should not have intestinal first pass
effect and should not induce (or) inhibit metabolism are good candidates for sustained release dosage forms.

**Margin of Safety**

Larger the values of therapeutic index, safer are the drug. Drugs with less therapeutic index are usually poor candidates for formulation of oral controlled drug delivery systems due to technological limitations of control over release rates.

**Plasma Concentration response relationship**

Generally pharmacological response of drug depends on plasma drug depends on plasma drug concentration rather than dose. But pharmacological activity of some drugs is independent of plasma concentrations, which are poor candidate for oral controlled release drug delivery system. E.g. Reserpine.

**Concentration Dependency on Transfer of Drug**

Transfer of drug from one compartment to other if follows zero kinetic process then such drugs are poor candidate for oral controlled release delivery system, it should be first order kinetics.

**MATRIX TABLETS**

One of the least complicated approaches to the manufacture of controlled release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression. Matrix tablets is a promising approach for the establishment of extended release drug therapy as tablets offer the lowest cost approach to sustained and controlled release and sustained release solid dosage forms.[20].

**Introduction**

*Matrix tablets* may be defined as the “oral solid dosage forms in which the drug (or) active ingredient is homogeneously dispersed throughout the hydrophilic (or) hydrophobic matrices which serves as release rate retardants [21]”. These systems release drug in continuous manner by dissolution-controlled and diffusion-controlled mechanisms. Under gastric pH conditions, matrix tablet slowly erodes. However at a pH corresponding to the upper small intestine, the tablet disintegrates rapidly to reduce coated particles, which in turn slowly releases drug. Two different
release mechanisms are operative, either of which is zero order erosion and decreasing surface area, and dissolution of coated particles, but the overall tablet release profile comprising the two mechanisms in sequence is nearly linear for most of the dose in the tablet. The result in the ability to control active pharmaceutical ingredient’s blood level’s in a narrow range, above the minimum effective level and below toxic level [22].

**Advantages offered by Matrix Tablets:** [20]

- Maintains therapeutic concentrations over prolonged periods.
- Avoids the high blood concentration.
- Reduction in toxicity by slowing drug absorption.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Better drug utilization.
- Minimize drug accumulation with chronic dosing.
- Reduction in health care cost.
- Improved patient compliance.
- Usage of less total drug.

**Disadvantages of Matrix Tablets:** [20]

- The remaining matrix must be removed after drug has been released.
- Greater dependence on GI residence time of dosage form.
- Delay in onset of drug action.
- Release rates are affected by food and the rate transit through the gut.

**Types of Matrix Tablets**

On the basis of polymer (or) release rate retardant used matrix tablets may be divided into following types [21, 23]

1. Hydrophilic Matrix Tablet.
2. Hydrophobic Matrix Tablet.
3. Fat-wax Matrix Tablet.
1. Hydrophilic Matrix Tablets

Hydrophilic matrix systems are presently one of the most interesting drug delivery systems. They are most widely used to control the release rate of drugs because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. Hydrophilic matrix tablets may be defined as the “Homogenous dispersion of drug molecules within a skeleton of hydrophilic polymers such as cellulose derivaties, xanthan gum, and etc. that swells upon contact with water”. These systems are called swellable-controlled release systems. Apart from swelling and diffusion mechanisms polymer dissolution is another important mechanism that can modulate the drug delivery rate. Swelling (or) dissolution can be the predominant factors for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these mechanisms. Granulation prior to mixing and the coating of matrix tablets are complementary operations widely used to manufacture matrix tablets. As well as the drug and the release-limiting polymer, other excipients are usually added as diluents, lubricants and antiadhearents.

2. Hydrophobic Matrix Tablets

The concept of using hydrophobic (or) inert materials as matrix materials was first introduced in 1959. In this method of obtaining controlled release from an oral dosage form, drug is mixed with an inert (or) hydrophobic polymer and then compressed into a tablet. Release is usually delayed because of dissolved drug has to diffuse through capillary network between the compacted polymer particles. This is the only system where the use of polymer is not essential to provide controlled drug release, although insoluble polymers have been used. The primary rate controlling components of hydrophobic matrices include waxes, glycerides, polyethylene, polyvinyl chloride, ethyl cellulose and etc. The rate controlling step in these formulations is liquid penetration into the matrix. The possible mechanism of release of drug in such types of matrix tablets is diffusion. Such types of matrix tablets become inert in the presence of water and gastrointestinal fluid. The presence of insoluble ingredient in the formulations helps to maintain the physical dimension of the hydrophobic matrix during drug release. Hydrophobic matrix systems are not suitable for gradient is too low to render adequate drug release.

3. Fat-Wax Matrix Tablets

The drug can be incorporated into fat wax granulation by spray congealing in air, blend congealing in the aqueous media with (or) without the aid of surfactants and spray-drying techniques. In the

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bulk congealing method, a suspension of drug and melted fat-wax is allowed to solidify and then
it is communicate for controlled-release granulation. The mixture of active ingredients, waxy
materials and fillers also can be converted into granules by compacting with roller compactor,
heating in a suitable mixture such as fluidized-bed and steam steam jacted blender (or)
granulating with a solution of waxy material (or) other binders. The drug embedded into a melt of
fats and waxes is released by leaching and (or) hydrolysis as well as dissolution of fats under the
influence of enzymes and pH change in the GIT. The addition of surfactants to the formulation
can also influence both the drug release and the proportion of total drug that can be incorporated
into a matrix.

4. Bio-degradable Matrices
These consist of the polymers which comprised of monomers linked to one other through functional groups and have unstable linkage in the backbone. It is biologically degraded (or) eroded by enzymes generated by surrounding living cells (or) by non enzymatic process into olegomers and monomers that can be metabolized (or) excreted. Examples are natural polymers such as proteins, polysaccharides and modified natural polymers, synthetic polymers such as aliphatic poly (esters) and poly anhydrides.

5. Mineral Matrices
These consist of polymers which are obtained from various species of sea weeds. Example is Alginic acid which is a hydrophilic carbohydrate obtained from species of brown seaweeds (Phaeophyceae) by the use of dilute alkali.

**On the basis of porosity matrix tablets may be divided into following types** [21]

- Macro Porous System
- Micro Porous System
- Non-Porous System.

1. **Macro Porous Systems**
In such systems, the diffusion of drug occurs through pores of matrix, which are of size range 0.1 to 1 µm. this pore size is larger than diffusing molecules size.

2. **Micro Porous System**
Diffusion in this type of systems occurs essentially through pores. For micro porous systems, pore size ranges between 50-200 Å, which is slightly larger than diffusing molecules size.
3. Non-Porous System

Non-porous systems have no pores and the molecules diffuse through the network meshes. In this case, only the polymeric phase exists and no pore phase is present.

**Table 2: Classification of Matrix Systems**

<table>
<thead>
<tr>
<th>Type of the Matrix System</th>
<th>Mechanism</th>
</tr>
</thead>
</table>
| Hydrophilic               | - Unlimited swelling delivery by diffusion  
                        | - Limited swelling controlled delivery  
                        | e.g.: Hydroxyl Ethyl Cellulose, Hydroxyl Propylmethyl Cellulose |
| Hydrophobic (or) Inert    | - Inert in nature  
                        | - Controlled delivery by diffusion  
                        | eg: Ethylcellulose |
| Fat- wax Matrix (or) Lipidic | - Delivery by diffusion & erosion  
                            | e.g.: Carnauba wax. |
| Biodegradable             | - Non lipidic nature  
                        | - Controlled delivery by surface erosion |
| Resin Matrices            | - Drug release from drug-resin complex  
                        | e.g.: Ion exchange resins |

Matrix systems can also be divided into three types

- Monolithic Matrix Tablets
- Gel forming hydrophilic Matrix Tablets
- Erodible (hydrophobic) Matrix Tablets.

**Inert monolithic Matrix Tablets** [24, 25]

Probably the simplest method of obtaining controlled release of a drug from an oral dosage form is incorporation of a drug in an inert matrix. In this case inert means matrix does not interact with the biological fluids. The main reason for its popularity is that drug release from plastic matrix tablets is independent on the state and condition of the digestive juices, which may show large inter- and intra patient variability (pH, viscosity). During its transit through the gastro-intestinal tract, the porous matrix tablet does not disintegrate like conventional tablets, but remains intact and the skeleton can be recovered in feces. The materials used in the preparation of these inert matrices are predominantly (insoluble) polymers and lipophilic compounds. The first polymers to be used for the preparation of matrix tablets were (semi-) synthetic polymers such as polyethylene, polyvinyl chloride, polymethyl methacrylate, polystyrene, poly vinyl acetate, cellulose acetate and ethyl cellulose. The fat compounds used included carnauba wax,
hydrogenated castor oil, and tristearin. Major drawback of most of the inert polymeric matrix tablets were their inherent first order drug release characteristics, their poor direct compression characteristics and the problematic cleaning of agglomeration equipment used for the preparation of agglomerates with the required compression characteristics.

1. Mechanism of Release of Inert Monolithic Matrix Tablet
Release from inert matrix tablets occurs via a leaching mechanism. Drug particles dispersed in the polymer matrix dissolve in the penetrating gastro-intestinal fluids and are released from the tablet by diffusion through the porous network of already existing pores and pores that created by dissolution of the drug particles. At drug loadings exceeding approximately 10-15 % volume, a continuous structure connecting all drug particles exists (percolating drug network). At considerably lower loadings, a particular fraction of the drug may be completely surrounded by the polymer matrix (trapped fraction), which would result in incomplete release.

2. Solvent Activated Matrix Tablets
The use of solvent-activated matrix tablets as a method to obtain zero order release i.e. constant release rates over an extended period was first proposed by Hoffenberg. Solvent-activated drug delivery system is a collective term comprising those systems in which the interaction between polymer and water is responsible for achieving controlled release. The interaction with water may include plasticization, swelling, dissolution, erosion or degradation of the polymer. The two most important types of solvent activated matrix tablets are gel-forming hydrophilic matrix tablets and erodible (hydrophobic) matrix tablets.

Gel-forming Hydrophilic Matrix Tablets [24, 25]
Gel-forming hydrophilic or swellable matrix systems are homogeneous or heterogeneous systems in which the drug is dispersed in a swellable hydrophilic polymer. These systems have been widely studied by researchers since they offer the possibility to obtain a constant drug delivery over an extended period of time. Drug release is a function of the polymer characteristics. Upon swallowing gel-forming hydrophilic matrix tablets, the hydrophilic polymer is plasticized by the aqueous gastro-intestinal due to which undergoes macromolecular chain relaxation and volume expansion. Consequently, upon penetration of the gastro-intestinal fluids into tablet, a sharp front can be distinguished which separates a dry, glassy core from a hydrated and rubbery gel layer. Release is governed by diffusion of the dissolved drug through the swollen gel layer and generally
shows a burst effect, caused by dissolution and leaching of drug particles present at the surface prior to formation of the release-controlling gel. Other swellable polymers, which have been applied in swelling-controlled oral drug delivery systems, which show solvent controlled release, are guar gums, xanthan gum, poly (ethylene oxide) (PEO), poly (vinyl alcohol), ethylene-vinyl alcohol copolymers (EVA) and dextrans.

**Erodible Matrix Tablets [25]**

Erodible polymers such as polyanhydrides offer another interesting material platform for zero-order drug release. Like several HPMC grades, upon water penetration, polyanhydrides form a gel-layer, which erodes at a specific rate. By choosing the right polymer composition the thickness of the gel-layer may remain constant with time resulting in a constant release rate until depletion of the drug. In the last two decades, controlled-release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Preparation of drug-embedded matrix tablet that involves the direct compression of a blend of drug, retardant material and additives is one of the least complicated approaches for delivering drug in a temporal pattern into the systemic circulation. The matrix system is commonly used for manufacturing controlled release dosage forms because it makes such manufacturing easy. A wide array of polymers has been employed as drug retarding agents each of which presents a different approach to the matrix concept. Polymers forming insoluble or skeleton matrices constitute the first category of retarding materials, also classed as plastic matrix systems. The second class represents hydrophobic and water-insoluble materials, which are potentially erodible; while the third group includes polymers those form hydrophilic matrices. Plastic matrix systems, due to their chemical inertness and drug embedding ability, have been widely used for controlling the release of the drug. Liquid penetration into the matrix is the rate-limiting step in such systems unless channeling agents are used. The hydrophobic and waxy materials, on the other hand, are potentially erodible and control the release of drug through pore diffusion and erosion. Polymers belonging to hydrophilic matrix systems, when exposed to an aqueous medium, does not disintegrate, but immediately after hydration develops a highly viscous gelatinous surface barrier, which controls the drug release from, and the liquid penetration into the center of the matrix system.
Drug Release from Matrix System [26, 23, 20]

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 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 bathing solution provides sink conditions at all times.

The release behavior for the system can be mathematically described by the following equation:

\[
\frac{DM}{Dh} = \frac{Co}{2} \cdot Dh - Cs/
\]

Where;

\[DM = \text{Change in the amount of drug released per unit area}\]

\[Dh = \text{Change in the thickness of the zone of matrix that has been depleted of drug}\]

\[Co = \text{Total amount of drug in a unit volume of matrix}\]

\[Cs = \text{Saturated concentration of the drug within the matrix.}\]

Additionally, according to diffusion theory:

\[
DM = \frac{(Dm \cdot Cs)}{h} \cdot Dt
\]

Where;

\[Dm = \text{Diffusion coefficient in the matrix.}\]

\[h = \text{Thickness of the drug-depleted matrix}\]

\[Dt = \text{Change in time}\]

By combining equation 1.3 and equation 1.4 and integrating:
When the amount of drug is in excess of the saturation concentration, then:

\[ M = [2Cs\cdot Dm\cdot Co\cdot t] \]  

Equation 1.5 and equation 1.6 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores.

The volume and length of the openings must be accounted for in the drug release from a porous or granular matrix:

\[ M = [Ds\cdot Ca\cdot p/T\cdot (2Co - p.Ca)\cdot t]^{1/2} \]  

Where:

- \( p \) = Porosity of the matrix
- \( t \) = Tortuosity
- \( Ca \) = solubility of the drug in the release medium
- \( Ds \) = Diffusion coefficient in the release medium.
- \( T \) = Diffusion path length.

For pseudo steady state, the equation can be written as:

\[ M = [2D.Ca\cdot Co\cdot (p/T)\cdot t]^{1/2} \]  

The total porosity of the matrix can be calculated with the following equation:

\[ p = pa + Ca/\rho + Cex/\rho ex \]  

Where:

- \( p \) = Porosity
- \( \rho \) = Drug density
- \( pa \) = Porosity due to air pockets in the matrix
- \( \rho ex \) = Density of the water soluble excipients

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Cex = Concentration of water soluble excipients.

For the purpose of data treatment, equation 1.9 can be reduced to:

\[ M = k \cdot t^{\frac{1}{2}} \] \quad (1.10)

Where

K is a constant, so that the amount of drug released versus the square root of time will be linear, if the release of drug from matrix is diffusion-controlled. If this is the case, the release of drug from a homogeneous matrix system can be controlled by varying the following parameters:

- Initial concentration of drug in the matrix
- Porosity
- Tortuosity
- Polymer system forming the matrix
- Solubility of the drug.

**Basic Principle of Drug Release** [27]

In solution, drug diffusion will occur from a region of high concentration to the region of low concentration. This concentration gradient is the driving force for the drug diffusion, out of a system. Water diffuses into the system in analogous manner. There is an abundance of water in the surrounding medium and system should allow water penetration. The inside of the system has low water content initially than the surrounding medium.

**Mechanism of Drug Release from Matrix Tablets** [28]

As shown in Figure 8, in erodible matrices, polymer erosion from the surface of the matrix determines the drug release, whilst in hydrophilic matrices, formation of the gel layer and it’s dynamic as a function of time determines the drug release. Gel layer thickness, which determines the diffusion path length of the drug, corresponds to the distance between the diffusion and erosion fronts. As the swelling process proceeds, the gel layer gradually becomes thicker, resulting in progressively slower drug-release rates. However, due to continuous hydration, polymer disentanglement occurs from the surface of the matrix, resulting in a gradually decreasing depletion zone and an increased dissolution rate.
Fig. 8: Schematic drug release from matrix of controlled-release drug delivery systems

(a) An erodible polymer matrix, and
(b) A Hydrophilic, swellable polymer matrix.

**Drug Release Kinetics - Model Fitting of the Dissolution Data** [29, 30]

Whenever a new solid dosage form is developed (or) produced, it is necessary to ensure that drug dissolution occurs in an appropriate manner. The pharmaceutical industry and the registration authorities do focus, nowadays, on drug dissolution studies. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug \( Q_0 \) is a function of the test time, \( t \) (or) \( Q = f(t) \). Some analytical definitions of the \( Q(t) \) are commonly used, such as

- Zero order,
- First order,
- Hixson-Crowell,
- Higuchi,
- Korsmeyer-Peppas models.

Different models expressing drug release kinetics were given in table 4.

**Zero Order Kinetics**

\[
Q_t = Q_0 + K_0 t
\]

\[\text{........... (1.11)}\]

Where:

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$Q_t$ is the amount of drug dissolved in time $t$,

$Q_0$ is the initial amount of drug in the solution (most times, $Q_0 = 0$)

$K_o$ is the Zero order release constant.

\[
f_t = K_o t \quad \text{........... (1.12)}
\]

\[
f_t = 1 - (W/W_0) \quad \text{........ (1.12)}
\]

Where;

$f_t$ represents the fraction of drug dissolved in time ($t$), and rate constant ($K_o$) the apparent dissolution rate constant (or) zero order release constant. In this way, a graphic of the drug-dissolved fraction versus time will be linear if the previously established conditions were fulfilled.

**Use:** This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with soluble drugs, coated forms, osmotic systems, etc. the pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action.

**First Order Kinetics**

Kinetic equation for the first order release is as follows

\[
\text{Log} Q_t = \text{log } Q_0 + K_t/2.303 \quad \text{........... (1.14)}
\]

Where

$Q_t$ is the amount of drug released in time ($t$),

$Q_0$ is the initial amount of drug in the solution

$K_t$ is the first order release constant.

In this way a graphic of the decimal logarithm of the released amount of drug versus time will be linear. The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release the drug in a way that is proportional
to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

**Higuchi Model** [31]

\[
q = Q = K_H \cdot t^{1/2} \quad \text{........... (1.15)}
\]

Where

\(K_H\) is the Higuchi dissolution constant

Higuchi dissolution constant treated sometimes in a different manner by different authors and theories. Higuchi describes drug release as a diffusion process based in the Fick’s law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water-soluble drugs.

**Hixson-Crowell Model**

Hixson and Crowell (1931) recognizing that the particle regular area is proportional to the cubic root of its volume derived an equation that can be described in the following manner.

\[
W_0^{1/3} - W_t^{1/3} = K_s \cdot t \quad \text{........... (1.16)}
\]

Where:

\(W_0\) is the initial amount of drug in the pharmaceutical dosage form,

\(W_t\) is the remaining amount of drug in the pharmaceutical dosage at time \(t\),

\(K_s\) is a constant incorporating the surface-volume relation.

This expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time. A graphic of the cubic root of the unreleased fraction of drug versus time will be linear if the equilibrium conditions are not reached and if the geometrical shape of the pharmaceutical dosage form diminishes proportionally over time. This model has been used to describe the release profile keeping in mind the diminishing surface of the drug particles during the dissolution.
Mechanism of Drug Release [32]

To understand the mechanism of drug release mechanism of pharmaceuticals due to swelling (upon hydration) along with gradual erosion of the matrix. Korsmeyer–Peppas model which is often used to describe the drug release behavior from polymeric systems when the mechanism is not well-known (or) when more than one type of release phenomena is involved.

\[
\log \left( \frac{M_t}{M_\infty} \right) = \log K_{KP} + n \log t \quad \text{........... (1.17)}
\]

Where;

\( M_t \) is the amount of drug release at time \( t \),

\( M_\infty \) is the amount of drug release after infinite time,

\( K_{KP} \) is release rate constant incorporating structural and geometrical characteristics of the tablet, and \( n \) is the release exponent indicative of the mechanism of drug release.

### Table 3: Drug Release Kinetics

<table>
<thead>
<tr>
<th>Kinetic Model</th>
<th>Relation</th>
<th>Systems Following the Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>First order</td>
<td>[ \ln Q_t = \ln Q_o + K_t ] (release is proportional to amount of drug remaining)</td>
<td>Water-soluble drugs in porous matrix</td>
</tr>
<tr>
<td>Zero order</td>
<td>[ f_t = K_o t ] (independent of drug concentration)</td>
<td>Transdermal systems Osmotic systems</td>
</tr>
<tr>
<td>Higuchi</td>
<td>[ f_t = K_H t^{1/2} ] (proportional to square root of time)</td>
<td>Matrix formulations</td>
</tr>
<tr>
<td>Hixson-Crowell</td>
<td>[ W_o^{1/3} - W_t^{1/3} = K_s t ]</td>
<td>Erodible isometric matrices</td>
</tr>
</tbody>
</table>

\( f_t = \text{fraction of dose release at time} \ 't' \);  
\( K_H, K_o, \text{and} \ K_s = \text{release rate constants characteristic to respective models} \);  
\( Q_o = \text{the drug amounts remaining to be released at zero hour} \);  
\( Q_t = \text{the drug amounts remaining to be released at time} \ 't'. \)  
\( W_o = \text{initial amount of drug present in the matrix} \);  
\( W_t = \text{amount of drug released at time} \ 't'. \)
CONCLUSION

The present review mentions about controlled drug delivery. Most used dosage form are solid, extended drug delivery plays prominent role. As they going to useful for the treatment of chronic disorders and diseases because the less frequency of administration this avoids the missing of dose.

REFERENCES


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