

## A review of medicines with sustained release

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### Abstract

Sustained-release matrix tablets allow for continuous drug release while also optimizing a drug's biologic, pharmacokinetic, and pharmacodynamic properties for maximum therapeutic efficacy. The matrix regulates the rate at which the drug is released. Because it facilitates prolonged release, the major excipient in the formulation is a release retardant. The technology may promote patient compliance and efficiently treat chronic illnesses by decreasing the overall dosage and dosing schedule. The drug is supplied in this system via diffusion- and dissolution-controlled methods. The primary goal of this analysis is to provide comprehensive information on the sustained release system and to discuss the many selection criteria for medicines used in medication administration system

**Keywords:** Sustained; Matrix; Tablets; Dissolution; Diffusion; Drug

### 1 Introduction

Oral drug delivery is the most commonly utilized method for systemic drug administration via pharmaceutical products of different dose types. The oral route is considered to be the most natural, convenient, and secure due to its ease of administration, patient compliance, and cost-effective production method. In terms of a drug's bioavailability, the rate at which it dissolves from its dosage form is critical consideration. The velocity of the bio-membrane of drug penetration impacts how rapidly orally administered hydrophilic medicines are absorbed.

In other words, the velocity of transmembrane transport or permeability restricts the absorption of such drugs. Pharmaceuticals intended for oral administration often employ conventional drug delivery techniques, which are designed for rapid drug release and absorption<sup>1</sup>.

- Due to the fact that short half-lives necessitate frequent administration, it is more likely that a patient would miss a dose, resulting in poor patient compliance.
- Plasma concentration-time profiles are frequently peak-valley, making it difficult to reach steady-state conditions.
- As the CSS values fall or rise outside the therapeutic range, unavoidable fluctuations in drug concentration may result in under- or overmedication.
- When a patient is overmedicated, the changing drug levels may have adverse effects, especially if the substance has a low therapeutic value.

To overcome the deficiencies of conventional drug delivery systems, a new drug delivery system that potentially revolutionize the administration of medicine and offer numerous therapeutic benefits has been created.

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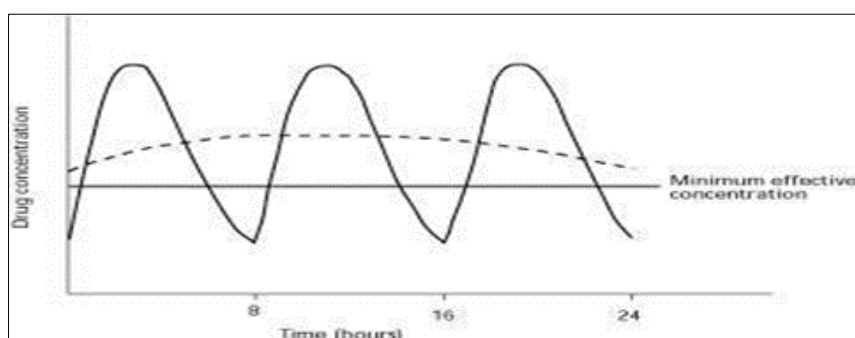
## 1.1 Modified drug delivery systems

- The term "modified-release dosage forms" refers to products that modify the timing and rate of drug material release. A modified-release dosage form is "one for which the drug release characteristics of time course and/or location are selected to achieve therapeutically or conveniently objectives not afforded by standard dosage forms such as solutions, ointments, or rapidly dissolving dosage forms." The USP/NF now recognizes multiple types of dose forms with modified release.
- Oral dosage forms: Modified-release dosage forms, Sustained release e.g. controlled release, sustained release, and prolonged release, Delayed release e.g. enteric-coated tablets.
- Intramuscular dosage forms: Depot injections, Water-immiscible injections e.g. oils
- Subcutaneous dosage forms: Implants

### 1.1.1 Transdermal delivery systems: Patches, creams, etc.

## 1.2 Sustained release dosage forms

In order to achieve and maintain optimal therapeutic blood levels, sustained release dosage forms are designed to release their medication at a predetermined rate, for a predetermined duration of time, and in a specific location. Sustained-release, slow-release, controlled-release, and prolonged-release are examples.



**Figure 1** Theoretical drug concentration profile following multiple dosing of a drug as an immediate-release form every 8 hours (–) as a sustained-release form once every 24 (–) hours

### 1.2.1 Advantages

There are three possible advantages of sustained-release products: sustained blood levels, mitigation of undesirable effects, and improved patient compliance.

- Sustained blood levels: Quantity and frequency of administration are determined by the drug's pharmacokinetic and pharmacodynamic properties. The slower the rate of absorption, the less the blood concentrations fluctuate over a treatment interval, making it easier to deliver larger dosages less frequently. For pharmaceuticals with relatively short half-lives, sustained-release formulations may assist maintain therapeutic concentrations for an extended period of time.
- Attenuation of adverse effects: With conventional dosage forms, high peak blood concentrations may be obtained rapidly after administration, and the transiently high concentrations themselves may have adverse consequences. Hypotension in patients getting nifedipine medicines with fast release is one example. By using a medicine with sustained-release, patients can avoid the high initial blood concentrations that cause reflex tachycardia and other severe hemodynamic abnormalities, such as a sudden drop in blood pressure. Another example is transient nausea at sub-toxic doses, which is caused by the local irritation caused by conventional-release medicines with high intestinal concentrations, such as theophylline. (3,4)
- Improved patient compliance: Short half-life drugs usually require frequent delivery to maintain therapeutic blood concentrations. The relationship between dose frequency and patient compliance is inverse. It is possible to reduce the number of daily doses delivered by sustained-release drugs, which could boost compliance. This advantage likely applies only when conventional formulations must be administered three or more times per day. (5)

### 1.2.2 Disadvantages

- Food and the rate at which a medication travels through the intestines can impact the rate of release of many pharmaceuticals with controlled release. There may be some fluctuation in the rate of release from one dose to

the next, but recent formulations have minimized these differences. Because sustained-release drugs include a higher drug load, any degradation in the release qualities of the dosage form could cause problems. Some sustained-release drugs may be divided into half-doses, whilst others must be taken in their whole. Never crush or chew modified-release products, as the slow-release features could be lost and injury could occur. This is essential for patients who struggle to take all of their medications, a common problem among the elderly. The larger size of sustained-release medications may make them more difficult to swallow or move through the digestive tract.

### 1.2.3 Medications suited to formulations with continuous release

The steady-state concentration of a drug fluctuates according to the relative magnitude of the elimination half-life and the dose interval. If a drug is delivered at intervals equal to its elimination half-life, the steady-state maximum and minimum concentrations vary by a factor of two. For drugs with short half-lives (3-6 hours) and a strong link between concentration and response, it will be essential to dose at regular, frequent intervals in order to maintain therapeutic concentrations. Higher dosages delivered at fewer regular intervals will yield greater peak concentrations with the potential for harm. This method may be useful for certain drugs with wide safety margins, such as amoxicillin, which has an 8-hour dosage interval despite a half-life of approximately one hour. As long as the concentrations remain above the minimum effective concentration throughout the dosing period, this technique poses no concerns due to the drug's low toxicity. On the other hand, drugs having long half-lives (>8 hours) can be delivered less often. Unless a rapid rate of concentration change during the absorptive phase is the cause of transient unpleasant effects, there is often no advantage to developing these drugs as sustained-release formulations. Multiple mechanisms support the pharmacological activity of a number of drugs with short half-lives:

- The medicine binds to tissues, such as ACE inhibitors that are tissue-bound. Despite the likelihood of a short half-life, numerous drugs require dosing less frequently.
- The drugs have lasting side effects, such as the inhibition of platelet cyclooxygenase by aspirin.
- The drug is transformed to one or more pharmacologically active metabolites, such as quinapril, trandolapril, or venlafaxine, which are eliminated more slowly from the body than the parent drug. (5,6)

### 1.2.4 Sustained release product design

The rationale for SR medication release

Dissolution and diffusion-controlled systems have traditionally played a crucial role in the oral delivery of medication<sup>4</sup> because to their relative price and ease of fabrication in comparison to other kinds of sustained or controlled distribution. Despite the recent introduction of a few liquids and suspensions, the majority of these systems are solids. These systems fall into the following categories:

- Dissolution-controlled release system.
- Diffusion-controlled release system.
- Osmotic pump system.
- Erosion-controlled release systems.

Dissolution controlled release systems

In dissolution-controlled sustained release systems, the rate at which drugs or other substances dissolve in the digestive juice regulates the rate of release. It is possible to increase the drug's solubility by producing soluble salts or derivatives. Utilizing a slowly dissolving vehicle to absorb the medication is an alternative way for obtaining sustained release via dissolution. Dissolution-controlled sustained release systems can be made by covering drug particles with a coating that dissolves slowly. Two phases are involved in the drug's release from such units.

- The liquid surrounding the releasing unit dissolves the covering (rate limiting dissolution step).
- The solid drug dissolves when it comes into touch with the liquid. Dissolution is the rate-limiting stage for the simplest oral drugs to prepare for prolonged release.

A substance with a slow rate of disintegration is sustained by its very nature. These drugs include salicylamide, griseofulvin, and digoxin, as examples. Producing the correct salt or derivative can decrease the solubility of drugs with high water solubility and, consequently, high dissolution rates. Unfortunately, due to their diminishing surface area over time, these structures do not meet the constant availability rate criteria. Continuous drug release can be achieved by coating drug particles or granules with substances of varying thicknesses or dispersing them in a polymer. This is the core principle of dissolution control. If the dissolution process is diffusion layer controlled and the rate of diffusion from the solid surface through an undisturbed liquid film to the bulk solution is rate limiting, the flux  $J$  is defined by the following equation:

$$J = -D (dc/dx)$$

Where D is the diffusion coefficient and  $dc/dx$  is the concentration gradient from the solid surface to the bulk solution. The flux can also be defined as the flow rate to material ( $dm/dt$ ) through a unit area (A), thus above equation can be written as

$$J = (1/A) dm/dt$$

If the concentration gradient is linear and the thickness of the diffusion layer is h,

$$dc/dx = (C_b - C_s)/h$$

Where  $C_s$  is the concentration at the solid surface and  $C_b$  is the concentration in the bulk solution. By combining the above equation, the flow rate of material is given by  $dm/dt = -(DA/h)(C_b - C_s) = kA(C_s - C_b)$  Where k is the intrinsic dissolution rate constant.

The above equation predicts a constant dissolution rate if the surface area, diffusion coefficient, thickness of the diffusion layer, and concentration difference remain constant. However, as the disintegration continues, all parameters, and surface area in particular, may change. The optimal dose form for this mechanism is compressed tablets containing particles with a coating.

Resins such as Ethylcellulose, Nylon, and Acrylic. Release is dependent on the solubility of the drug and the membrane's pore structure. Constant release occurs as GI fluid goes through the barrier and dissolves the drug.

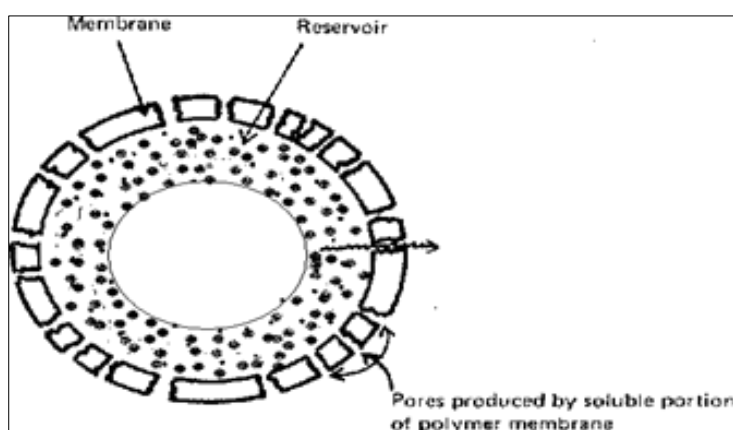
Diffusion Controlled Release: During the past two decades, two types of diffusion-controlled systems have been developed:

- Reservoir devices and 2. Matrix device

When the drug is in a solid (typically polymer) phase or in pores filled with gastric or intestinal fluids, the approach of controlling release is utilized.

On the basis of the area of the release unit in which drug diffusion occurs, diffusion-controlled release systems are classified as matrix systems (also known as monolithic systems) or reservoir systems.

In reservoir systems, diffusion occurs in a thin, water-insoluble film or membrane that frequently ranges in thickness from 5 to 20 micrometers and surrounds the release unit. In matrix systems, diffusion occurs in pores within the bulk of the release unit. Fluid can diffuse through the membrane's pores or its solid phase.



**Figure 2** Diffusion Control of Drug release by a Water-Insoluble Polymer

Following are the processes required to release a drug from a diffusion-controlled release unit.

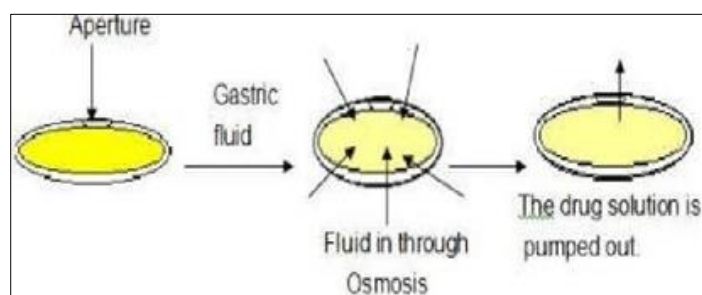
- The drug is dissolved by the surrounding liquid, which then enters the release unit.
- Consequently, there is a concentration gradient between the interior and exterior of the release device.

- The drug will permeate through the membrane pores surrounding the release unit or nearby tissue and be released
- Dissolved medication will seep into the membrane that surrounds the dosage unit.

Thus, the release procedure often involves a dissolving stage, but the diffusion step is the rate-controlling step. The rate of diffusion is determined by four factors: concentration gradients along the diffusion distance, area, the distance over which diffusion occurs, and the drug's diffusion coefficient in the diffusion medium. Several of these variables are incorporated into the formulation to regulate the release rate.

#### Osmotically powered system

In these products, the rate of drug release is determined by the steady flow of water over a semipermeable membrane into a reservoir holding an osmotic agent. Either the drug and agent are mixed together, or the drug is contained in a reservoir. The dosage form features a tiny hole through which the medication is pumped at a rate determined by the rate at which water enters the container due to osmotic pressure. The advantage of this type of drug is that the environment of the digestive tract has no effect on the controlled release. To alter the rate of discharge, both the osmotic agent and the hole size can be altered.



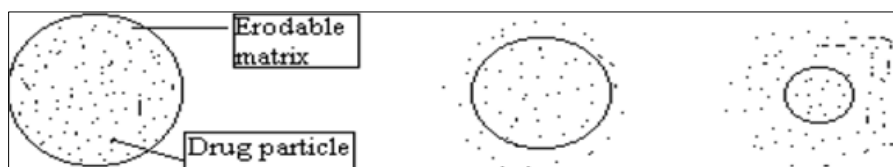
**Figure 3** Osmotic controlled system

$$dm/dt = Ak\pi ss/h$$

Where A =membrane area; k =membrane permeability; h =membrane thickness

#### Controlled release systems for erosion

In erosion-controlled sustained release systems, the rate of drug release is controlled by erosion of the matrix in which the drug is dispersed. Examples include lipids or waxes in which the drug is dispersed. Polymers that gel when exposed to water are another example (Hydroxy ethyl cellulose). As the gel erodes, the drug that has been dissolved or dispersed inside it will be released. Concurrent drug diffusion within the gel is possible. (7) . The diffusion and type matrix systems are notable among the previously discussed systems.



**Figure 4** Erosion-controlled release systems

### 1.3 Matrix devices:<sup>8</sup>

In these systems, drugs are dispersed uniformly throughout a polymer. According to this concept, the medication in the outer layer in touch with the bath solution first dissolves before diffusing out of the matrix. Higuchi has derived the following equation to reflect the rate of release of pharmaceuticals spread in an inert matrix system.

$$dm/dh = C_0 d h - C_s / 2.$$

Where,  $dm$ = Change in the amount of drug released per unit area,  $dh$ = Change in the thickness of the zone that has been depleted of the drug,  $Co$ = Total amount of drug in a unit volume of the matrix,  $Cs$ = Saturated concentration of drug within the matrix.

### 1.3.1 *There are various benefits to matrix systems*

Using this versatile and inexpensive method, molecules with a high molecular weight can be liberated. Cracks in the matrix material can occasionally result in the unintended release of the complete pharmacological component, although this occurrence is less often.

### 1.3.2 *The matrix systems' drawbacks*

After the drug has been released, the remaining matrix must be eliminated. The square root of time influences the rate of drug release. The release rate continuously decreases due to an increase in diffusional resistance and/or a decrease in the effective area at the diffusion front. Using extremely slow release rates, which in many instances are identical to zero-order, might provide a strong enduring effect.

## Classification of Matrix Tablets

The system can be divided into two categories depending on the types of retarding agents or polymeric materials

Based on the retardant material used

- Hydrophobic Matrices (Plastic matrices):<sup>9</sup>

Although insoluble polymers have been employed, this is the sole system where they are not required to achieve regulated drug release. The main rate-regulating elements of hydrophobia are, as the name implies, water-insoluble. Wax, glycerides, fatty acids, and polymeric substances including ethyl cellulose, methylcellulose, and acrylate copolymer are some of these constituents. It could be required to include soluble components like lactose in the formulation to control medication release. The physical dimension of hydrophobic is kept constant during medication release thanks to the inclusion of an insoluble component in the formulations. As a result, diffusion of active substances from the system is the release mechanism 8, and the Higuchi equation, also known as the square root of time release kinetic, can explain the corresponding release characteristic. With a porous monolith, where the release from such a system is proportionate to the drug loading, the square root of the temporal release profile is anticipated. Additionally, because the concentration gradient is too modest to allow for efficient drug release, hydrophobic matrix systems are typically not appropriate for an insoluble drug. As a result, partial medication release during gastrointestinal transit time is a possible concern that must be identified during the development process based on the actual constituent qualities or formulation design. In these formulations, liquid penetration into the matrix serves as the rate-controlling step. Diffusion is one potential method by which medications in these kinds of tablets are released. In the presence of water and gastrointestinal fluid, certain types of matrix tablets become inactive.

- Lipid Matrices:<sup>10</sup>

Lipid waxes and other similar substances are used to create these matrices. Drug release from these matrices happens via pore diffusion as well as erosion. Therefore, release properties are more susceptible to digestive fluid composition than a polymer matrix that is completely insoluble. Many sustained-release formulations have used carnauba wax as a retardant basis in conjunction with stearyl alcohol or stearic acid.

- Hydrophilic Matrices:<sup>11</sup>

In the realm of controlled release, there is special interest in the formulation of medications in gelatinous capsules or, more frequently, tablets using hydrophilic polymers with high gelling capabilities as the foundation. Swellable controlled release systems are what these systems are known as. Three broad categories of polymers are used in the creation of hydrophilic matrices.

- ✓ Cellulose derivatives: Methylcellulose 400 and 4000 CPs, hydroxyl ethyl cellulose, hydroxyl propyl methyl cellulose (HPMC) 25, 100, 4000, and 15000 cps, and sodium carboxy methyl cellulose.
- ✓ Non-cellulose natural or semi-synthetic polymers: Agar-agar, carob gum, alginates, molasses, polysaccharides of mannose and galactose; chitosan, and modified starches.
- ✓ **Polymers of acrylic acid:** Carbopol 71 G NF.

- Biodegradable Matrices:12

These are composed of polymers with unstable backbone linkages made up of monomers connected to one another by functional groups. They are physiologically eroded or broken down into oligomers and monomers that can be metabolized or expelled by enzymes produced by the live cells around them or by a non-enzymatic process. Examples include synthetic polymers such as aliphatic poly (esters) and poly anhydrides, as well as natural polymers like proteins and polysaccharides, as well as modified natural polymers.

- Mineral Matrices:(13-15)

These are made up of polymers derived from several seaweed species. Alginic acid is a good illustration. It is a hydrophilic carbohydrate that may be made from several brown seaweed species (Phaeophyceae) using diluted alkali.

Based on the porosity of matrix systems:

- Microporous system:

In such systems, the diffusion of the medication happens through pores in the matrix, which are in the size range of 0.1 to 1 $\mu$ m. This pore size is bigger than the molecule size that diffuses.

- Micro porous System:

In this kind of system, diffusion primarily takes place through pores. Pore sizes for microporous systems range from 50 to 200 Å, which is a bit bigger than diffusing molecule size.

- Non-porous System:

Molecules diffuse over the network meshes in non-porous systems because they lack pores. In this instance, there is simply the polymeric phase and no pore phase.

### 1.3.3 Polymers used in matrix tablets:(16-18)

**Table 1** list of polymers used in matrix tablets

Type	Examples
Hydrogels	Poly hydroxyl ethyl methyl acrylate (PHEMA), Cross-linked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone (PVP), Polyethylene oxide (PEO)
Soluble polymers	Polyethylene glycol (PEG), Polyvinyl alcohol (PVA), Polyvinyl pyrrolidone (PVP), Hydroxypropyl methylcellulose (HPMC), Polylactic acid (PLA)
Biodegradable polymers	Polyanhydrides, Poly-ortho-esters, Polyethylene vinyl acetate (PVA), polydimethylsiloxane (PDS), Polyether urethane (PEU)
Non-biodegradable polymers	Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC), Polycarbophil, Sodium carboxymethyl cellulose
Mucoadhesive polymers	Tragacanth, Methylcellulose, Pectin
Natural gums	Xanthan gum, Guar gum

### 1.3.4 Mechanism of drug release:19

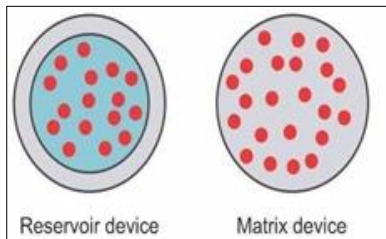
The medication in the outer layer that is in contact with the bathing solution dissolves initially before diffusing out of the matrix. The contact between the bathing fluid and the solid medication is still creeping inward during this procedure. As a result, for this system to function as a diffusion-controlled system, the rate at which drug particles dissolve within the matrix must be substantially higher than the rate at which the dissolved drug diffuses out of the matrix. The first law of diffusion by Fick governs the release from matrix-type formulations

$$J = dQ/dt = -D \, dC/dx$$

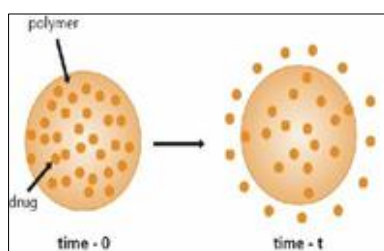
J is flux, or rate of diffusion, while Q is the amount diffused per unit of time t, and D is diffusion coefficient.

Theories that are based on Fick's law of diffusion distinguish two types of systems

- Reservoir and 2) matrix devices



**Figure 5** Schematic illustration of two types of diffusion-controlled spherical drug delivery devices



**Figure 6** Drug release from matrix devices

The release of drugs from a homogeneous matrix system can be controlled by varying the following parameters:

- The initial concentration of the drug in the matrix
- Porosity, Tortuosity, Polymer system forming the matrix, Solubility of the drug.

Fickian diffusional release and relaxation release are two competing drug release processes in a hydrophilic matrix. In addition to diffusion, the subsequent polymer relaxation's erosion also adds to the overall release of a medication from the matrix. The characteristics of a particular medicine will largely determine the relative contribution of each component to the overall release. For instance, a swelling-controlled diffusion process is used to release a sparingly soluble medication from hydrophilic matrices while yet allowing water to be absorbed. A glassy polymeric matrix expands when water seeps through it, lowering the glass transition temperature. The dissolved medicine diffuses into the external releasing media at the same time through this inflated, rubbery area. Typically, a Fickian diffusion mechanism is not followed by this kind of diffusion and swelling. To describe drug release behaviour from hydrophilic matrix systems, Peppas (1985) developed the following semi-empirical equation:

$$Q = k \cdot t^n$$

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

For n=0.5, drug release follows a Fickian diffusion mechanism that is driven by a chemical potential gradient.

For n=1, drug release occurs via the relaxational transport that is associated with stresses and phase transition in hydrated polymers.

For 0.5 < n < 1, Non-Fickian diffusion is often observed as a result of the contributions from diffusion and polymer erosion



To describe relaxational transport, introduced a second term in equation <sup>10</sup>

$$Q = k_1 t^n + k_2 t^{2n}$$

Where  $k_1$  and  $k_2$  are constants reflecting the relative contributions of Fickian and relaxation mechanisms.

In the case the surface area is fixed, the value of  $n$  should be 0.5 and the equation becomes:

$$Q = k_1 t^{0.5} + k_2 t$$

Where the first and second terms represent drug release due to diffusion and polymer erosion, respectively.<sup>20</sup>

#### 1.4 Drug characteristics pertinent to the formulation for sustained release: <sup>21</sup>

Each of the factors are interconnected, which places limitations on the options for distribution method, delivery system layout, and length of therapy. For the design of a sustained-release dosage form, a drug's characteristics are crucial. The drug's physicochemical and biological qualities are primarily what matter.

##### 1.4.1 Physicochemical Properties

Aqueous solubility and PKA:<sup>22</sup>

A drug must first dissolve in the aqueous phase surrounding the administration site before partitioning into the absorbing membrane in order to be absorbed. A drug's water solubility and, assuming it is a weak acid or basic, its PKA are two of the most crucial physicochemical characteristics that affect how well it is absorbed. The effectiveness of controlled release systems is influenced by these characteristics. A drug's aqueous solubility affects its rate of dissolution, which in turn determines its concentration in solution and, consequently, the force that propels diffusion through the membrane. The Noyes-Whitney equation demonstrates that the state under the sink is one where the dissolving rate is related to aqueous solubility.

$$dc/dt = KDAC_s$$

Where,  $dc/dt$  = Dissolution rate;  $KD$  = Dissolution rate constant,  $A$  = Total surface area of the drug particles;  $C_s$  = Aqueous saturation solubility of the drug.

The starting rate is directly proportional to aqueous solubility,  $C_s$ , and the dissolving rate is constant only if surface area 'A' remains constant. As a result, a drug's water solubility can be utilized as a preliminary estimate of its rate of dissolution. Low aqueous solubility drugs typically have issues with oral bioavailability and low dissolving rates. Weak acids and bases can dissolve in water depending on the pH of the medium and the pKa of the chemical.

For weak acid,

$$S_t = S_0 (1 + K_a / [H^+]) = S_0 (1 + 10^{pH - pK_a}) \dots (1)$$

Where,  $S_t$  = Total solubility (both ionized and un-ionized forms) of the weak acid,  $S_0$  = Solubility of the un-ionized form,  $K_a$  = Acid dissociation constant,  $H^+$  = Hydrogen ion concentration of the medium

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

For a weak base,

$$S_t = S_0 (1 + [H^+] / K_a) = S_0 (1 + 10^{pK_a - pH}) \dots (2)$$

Where,  $S_t$  = Total solubility (both conjugate acid and free base forms) of the weak base.  $S_0$  = Solubility of the free base form,  $K_a$  = Acid dissociation constant of the conjugate acid

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

In general, controlled-release medication formulations should avoid drugs with extremes in their water solubility. Dissolution-limited absorption and an inherently sustained blood level are characteristics of drugs with very low solubility and slow dissolution rates. A controlled-release approach for such a medicine might not offer many advantages over traditional dose forms. A weakly soluble medication would not be ideal for any system that relies on the diffusion of the drug through a polymer as the rate-limiting step in release, as the driving force for diffusion is the concentration of the drug in the polymer or solution, and this concentration would be low. It can be challenging to slow down the dissolution rate and increase the solubility of a medicine with a high dissolution rate. But one way to make controlled-release dose forms is to make a medicine that ordinarily has high solubility into a mildly soluble form.

Partition Coefficient:<sup>23</sup>

A range of lipid biological membranes that primarily serve as barriers must be crossed by a medicine before it can diffuse through them and be eliminated from the body. An important factor in determining whether a medicine may cross these lipid membranes is its apparent oil/water partition coefficient, which is calculated as

$$K=C_0 / C_w$$

Where,  $C_0$  = Equilibrium concentration of all forms of the drug e.g. ionized and unionized in an organic phase at equilibrium,  $C_w$  = Equilibrium concentration of all forms in the aqueous phase.

Drugs with exceptionally high K values are typically particularly oil soluble and quickly partition into membranes. The Haunch correlation states that there is a parabolic relationship between the logarithms of a drug's activity or absorption capacity and its partition coefficient. This connection can be explained by the idea that a drug's capacity to engage with a receptor and cross membranes determines how active it is. A drug's activity increases with how well it passes the membrane. The drug's ideal partition coefficient, which determines how well it may pass across membranes and exhibit the most activity. The K number at which the best activity is seen is roughly 1000/1. In general, medications that have a partition coefficient that is either higher or lower than the ideal make worse candidates for formulation into controlled-release dosage forms.

Drug stability

The loss of medications due to acid hydrolysis and/or metabolism in the GI tract is a significant factor for oral dose formulations. Considering that a medicine in the solid state degrades much more gradually than a substance in suspension or solution. A medicine that is unstable in the GI tract can have its relative bioavailability improved greatly by being given in a controlled release form that is released slowly over time. The best regulating unit would be one that only releases its material in the intestine for medications that are unstable in the stomach.

The opposite is true for medications that are unstable in the colon; in this situation, a regulating unit that releases its contents solely in the stomach would be most appropriate. In order to deliver their substance uniformly along the length of the GI tract, controlled release systems should not be formulated with medications that have major stability issues in any one region of the GI tract. Highly unstable pharmaceuticals may benefit from controlled drug delivery systems because the medication may be shielded from enzymatic degradation by inclusion into a polymeric matrix.

Protein binding:<sup>24</sup>

Some medications have a propensity to bind with plasma proteins (such as albumin) and produce drug retention in the circulatory space. Electrostatic, hydrogen-bonding, and Vander-Waals forces make up the major forces of attraction that cause binding. Due to electrostatic forces, charged substances typically have a stronger propensity to bind proteins than uncharged substances.

If a medicine attaches to a protein, the process of the drug's equilibrium separation from the protein controls how much of the drug is released into the extravascular space. Therefore, the drug-protein complex can act as a reservoir in the circulatory space for the controlled release of pharmaceuticals to extravascular tissues, but only for those medications that show a high level of binding. Thus, independent of the type of dosage form, a drug's ability to attach to proteins can have a substantial impact on how it works therapeutically.

Drugs with extensive binding to plasma proteins will typically have a lengthy half-life of elimination, negating the need for a controlled-release dose form. Medications that bind strongly to plasma protein may also bind to biopolymers in the GI tract, which could affect the delivery of controlled drugs. 11, 12.

### Molecular size and diffusivity

In many controlled-release systems, drugs must diffuse through a membrane or matrix that regulates their rate of diffusion. A drug's so-called diffusivity (diffusion coefficient), which refers to its capacity to disperse through membranes, depends on the molecular size of the medication (or molecular weight). The molecular weight (or size) of the diffusing species has a significant impact on the value of diffusivity, or "D," in polymers. It is possible to empirically link log D to some function of molecule size as follows for the majority of polymers:

$$\log D = -S_v \log V + K_v = -S_M \log M + K_m$$

Where,

V = Molecular volume, M= Molecular weight, S<sub>v</sub>, S<sub>M</sub>, K<sub>v</sub>, K<sub>m</sub> = constants.

The value of 'D' thus is related to the size and shape of the cavities as well as the size and shape of drugs. Generically, values of the diffusion coefficient for intermediate molecular weight drugs, i.e., 150 to 400. Flexible polymers range from 10<sup>-6</sup> to 10<sup>-9</sup> cm<sup>2</sup>/sec, with values on the order of 10<sup>-8</sup> being the most common. A value of approximately 10<sup>-6</sup> is typical for these drugs through the water as the medium. For drugs with a molecular weight greater than 500, the diffusion coefficient in many polymers frequently is so small that they are difficult to quantify, i.e., less than 10<sup>-12</sup> cm<sup>2</sup>/sec. Thus, high molecular weight drugs and/or polymeric drugs should be expected to display very slow-release kinetics in Controlled-release devices using diffusion through polymeric membranes or matrices as the releasing mechanism <sup>11</sup>.

#### 1.4.2 Biological Properties of Drug:<sup>25</sup>

Mechanism and Sites of Absorption:

For oral ER drug delivery systems, such as numerous B vitamins, drugs absorbed through a window or by carrier-mediated transport are poor options. For oral ER drug delivery systems, medications that are absorbed passively through pore transport, through the GIT's full length, or both are suitable choices.

Distribution

Oral ER drug delivery systems are not suitable for drugs with a high apparent volume of distribution, which affects the pace of drug clearance, such as chloroquine.

The half-life of Drugs

The optimum medication for an oral ER drug delivery system has a biological half-life of between 2 and 8 hours. Given that the biological half-life is 2 hours, the system will need an excessively high rate and dose. It is not necessary to formulate this medication for oral ER drug administration if the biological half-life is greater than 8 hours.

The margin of safety

As is common knowledge, the safer a medicine is, the higher its therapeutic index value. Due to technological restrictions on control over release rates, drugs with lower therapeutic indices are typically poor choices for formulation into oral ER drug delivery systems.

Plasma Concentration Response Relationship

Instead of size and dose, the medicine's pharmacological action typically rely on plasma drug concentration. However, some medications' pharmacological effects are not dependent on plasma concentrations, making them a poor choice for oral SR drug delivery systems. such as Reserpine

## 2 Conclusion

We can infer from the discussion above that sustained-release matrix tablets aid in resolving the issues with conventional dose forms. With this technique, the medication is released gradually. The sustained drug delivery system's design is influenced by a number of variables, including the disease being treated, the length of the course of therapy, and the state of the patient. Along with other benefits, this type of system's cost-effectiveness and once-daily dosage are among its main features. The dosage form design is being optimized using this system.

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## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest.

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