

# The Science of Sustained-Release Medications

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## ABSTRACT

Sustained release pharmaceutical products became a very useful tool in medical practice, actual and perceived advantages to the patients. Sustained release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. Sustained release system are considered a wiser approach for the drug with short half lives and which requires repeated dosing, they are easy to formulate and irrespective of absorption process from gastrointestinal tract after oral administration. Sustained systems include any drug delivery system that achieves slow release of drug over an extended period of time. Now a days as very few drugs are coming out of research and development and already existing drugs are suffering the problem of resistance due to their irritational use specifically in case of drug like antibiotics. The basic rationale of sustained release drug delivery system optimizes of the biopharmaceutical and pharmacokinetic and pharmacodynamics properties of the drug in such a way that utility is maximized, side effect reduced and cure of the disease is achieved. The principle goal of sustained release form is the improvements of drug therapy assessed by the relationship between advantages of the use of sustained release system. This article contains the basic information regarding sustained release formulation and also the different types of the same.

## INTRODUCTION

Sustained release refers to a pharmaceutical formulation designed drug molecules gradually over an designed to release drug molecules gradually over an extended period, maintaining therapeutic levels in the body[1]. This controlled release mechanism offers advantages such as prolonged drug action, reduced dosing frequency, improve patient compliance, and minimized fluctuation in drug concentration.

Sustained-release medication is a type of programmed release dosage form that contains multiple single doses of a drug. It is designed to release the drug over an extended period, thereby producing a prolonged clinical effect[2]. The primary rationale behind this approach is to optimize the drug's biopharmaceutic, pharmacokinetic, and pharmacodynamic properties, ultimately maximizing its utility by reducing side effects.

The oral route is the most commonly used method for drug administration due to its convenience and the flexibility it offers in dosage form design. Drug delivery systems such as sustained release, prolonged release, modified release, extended release, and depot formulations are designed to maintain therapeutic drug levels by releasing the active ingredient gradually over an extended period following a single dose[3]. This approach offers several advantages, including improved patient compliance and enhanced therapeutic efficacy, as it helps maintain more consistent plasma drug concentrations. Given the high costs and complexities involved in developing new drug entities, there is increasing focus on developing sustained or controlled-release formulations[4]. One of the most widely used methods for achieving sustained drug release is the matrix system. In this system, the drug is either dissolved or uniformly dispersed within a hydrophilic polymer matrix, which regulates its release over time. The ultimate goal of extended-release formulations is to maintain effective drug levels in the bloodstream for a prolonged period, reducing dosing frequency and improving treatment outcomes.

The rationale for the development of Sustained Release Drug Delivery Systems (SRDDS) is well-summarized in your points. Let's elaborate on each to provide a comprehensive understanding:

## **Rational for Development of SRDDS**

### **Prolonged Drug Action and Reduced Dosing Frequency:**

**Improved Clinical Efficacy:** Conventional immediate-release formulations often lead to fluctuating drug levels in the bloodstream, with peaks that can be too high (leading to toxicity) and troughs that are too low (leading to sub-therapeutic effects).[5] SRDDS aim to maintain a relatively constant drug concentration within the therapeutic window over an extended period. This steady availability at the action site throughout the treatment duration optimizes the drug's pharmacological effect, leading to improved clinical outcomes.

**Enhanced Patient Compliance:** Reducing the number of daily doses significantly improves patient adherence to the treatment regimen[6]. Patients are less likely to miss doses when they only need to take medication once or twice a day, compared to multiple times a day. This is particularly crucial for chronic conditions where long-term medication adherence is vital.

### **Reduced Cost of Treatment:**

While the initial manufacturing cost of an SRDDS might be slightly higher than a conventional formulation, the overall cost of treatment can be reduced[7]. This is primarily due to:

**Fewer Dosage Units:** Patients require fewer pills or administrations over the course of treatment, leading to a reduction in the total number of dosage forms purchased.

**Reduced Healthcare Resource Utilization:** Improved patient compliance and consistent therapeutic effects can lead to fewer treatment failures, hospitalizations, and doctor visits, thereby lowering overall healthcare costs.

### **Minimized Toxicity Due to Overdose:**

Conventional dosage forms, especially those with narrow therapeutic windows, carry a higher risk of dose dumping or accidental overdose if taken incorrectly or too frequently[8]. SRDDS are designed to release the drug gradually, preventing rapid spikes in drug concentration that can lead to adverse effects and toxicity. This controlled release mechanism helps to maintain drug levels within the safe and effective range, minimizing the risk of drug-related side effects[9].

### **Enhanced Activity Duration for Drugs with Short Half-Life:**

Drugs with short biological half-lives are quickly metabolized and eliminated from the body, necessitating frequent dosing with conventional formulations. SRDDS overcome this limitation by continuously releasing the drug, effectively extending its therapeutic presence in the body[10]. This negates the need for multiple daily doses, making the drug more practical for long-term use and improving its overall therapeutic utility. For example, if a drug has a half-life of 2-3 hours, a conventional formulation might require dosing every 4-6 hours. With an SRDDS, it might be possible to administer the drug once or twice a day.

In essence, the development of SRDDS is driven by the desire to optimize drug therapy, making it safer, more effective, more convenient for patients, and potentially more cost-effective in the long run[11]. They represent a significant advancement in pharmaceutical science, moving beyond simple drug delivery to controlled and targeted drug action and advantages.

**Long-Term Treatment for Chronic Diseases:** Many chronic conditions necessitate prolonged medication regimens. In such scenarios, lack of patient compliance is a major hurdle to successful drug therapy.

**Addressing Factors Affecting Adherence:** Patient adherence to a treatment regimen is a complex interplay of various factors, including:

**Awareness and Understanding:** A patient's understanding of their disease process and the rational e behind their prescribed therapy.

**Faith in Therapy:** The patient's belief in the effectiveness of the treatment.

**Understanding of Regimen:** Comprehension of the need to adhere to a strict treatment schedule.

**Complexity of Therapeutic Regimen:** The more complex a regimen (e.g., multiple daily doses, specific timing requirements), the more challenging it is for patients to follow consistently.

**Cost of Therapy:** Financial burden can impact a patient's willingness or ability to continue treatment.

**Side Effects:** The magnitude of local and/or systemic side effects associated with the dosage form can deter adherence.

### **How SRDDS Enhance Compliance:**

SRDDS directly address several of these compliance barriers, primarily by:

**Minimizing Dosing Frequency:** By reducing the number of daily doses (e.g., from three or four times a day to once or twice), SRDDS simplify the medication schedule. This reduced frequency makes it easier for patients to remember to take their medication, especially for busy individuals or those with memory challenges.

**Providing Consistent Therapeutic Levels:** The steady release of the drug ensures that therapeutic levels are maintained over an extended period, which can lead to more predictable and often better clinical outcomes. When patients perceive that their medication is consistently working and improving their condition, their faith in the therapy is strengthened, encouraging continued adherence.

**Potentially Reducing Side Effects:** As discussed in the rationale, SRDDS can reduce the "peak" concentrations of a drug that are often associated with dose-dependent side effects. By mitigating these uncomfortable or adverse effects, SRDDS can make the treatment more tolerable for the patient, thereby improving their willingness to comply.

In essence, by simplifying the dosing schedule and often leading to a more comfortable patient experience, Sustained Release Drug Delivery Systems play a pivotal role in **overcoming the problem of non-compliance**, ultimately contributing to better treatment outcomes and improved patient well-being.

## **DISADVANTAGES OF SUSTAINED RELEASE SYSTEM**

While Sustained Release Drug Delivery Systems (SRDDS) offer significant benefits, they also come with certain limitations that need to be carefully considered[12]:

### **Inhibition of Prompt Termination of Therapy**

A major drawback of SRDDS is the **difficulty in immediately stopping treatment** if necessary. Since the drug is designed to release slowly over an extended period, it's not possible to simply halt administration and expect the drug's effects to cease quickly.

**Adverse Effects:** If a patient experiences significant adverse effects or an allergic reaction, promptly removing the drug from their system is challenging. The sustained release mechanism means the drug will continue to be absorbed, potentially prolonging or worsening the adverse event, which cannot be easily accommodated.

### **Less Dosage Flexibility**

SRDDS offer **less flexibility in adjusting dosage regimens** compared to immediate-release formulations.

**Fixed Design:** The release profile and dosage are largely fixed by the design of the dosage form during manufacturing. This means physicians have limited ability to titrate the dose up or down rapidly based on individual patient needs or changing clinical conditions. Fine-tuning the medication to achieve optimal therapeutic levels for a specific patient can be more difficult.

### Patient Variation Not Fully Accommodated

Sustained release forms are typically designed for the "average" population, based on average drug biological half-lives and pharmacokinetic parameters.

**Individual Differences:** This standardization can be problematic because **significant patient variation** exists in drug disposition (how the body absorbs, distributes, metabolizes, and excretes a drug). Factors like disease states (e.g., liver or kidney impairment), genetic polymorphisms, age, and co-medications can drastically alter a drug's half-life and metabolism. SRDDS may not adequately accommodate these individual differences, potentially leading to sub-therapeutic levels in some or toxic levels in others.

### Economic Factors

The manufacturing process for many sustained release forms often involves **more costly processes and specialized equipment** compared to conventional immediate-release tablets or capsules.

**Higher Production Costs:** This can translate into higher overall production costs, which may be reflected in the final price of the medication. While potential long-term savings from improved compliance and reduced healthcare visits exist, the initial economic outlay for the drug itself can be higher.

### Poor In-Vivo and In-Vitro Correlations (IVIVC)

Achieving predictable drug release and absorption in SRDDS can be complex, sometimes leading to **poor correlations between in-vitro (laboratory) and in-vivo (within the body) performance**.

**Absorption Window Issues:** In sustained release dosage forms, the drug's release rate is deliberately reduced to allow it to be absorbed over a larger region of the gastrointestinal (GI) tract. However, some drugs have specific "absorption windows" – limited areas in the GI tract where they are efficiently absorbed. If the sustained release extends beyond this window, it can result in **unsatisfactory drug absorption in vivo**, despite the drug showing excellent release characteristics when tested in a lab setting. This can lead to variable bioavailability and unpredictable therapeutic effects.

### Risk of Dose Dumping

**Dose dumping** is a critical and potentially dangerous phenomenon associated with sustained release formulations.

**Rapid Release of Drug:** It occurs when a relatively large quantity of the drug intended for slow release is suddenly and rapidly discharged from the formulation into the systemic circulation.

**Potential for Toxicity:** This rapid release can introduce **potential toxic quantities of the drug** into the bloodstream. Dose dumping can be fatal, especially with **potent drugs that have a narrow therapeutic index** (where the therapeutic dose is very close to the toxic dose), such as Phenobarbital. This risk can arise from formulation defects, interactions with food or alcohol, or physical damage to the dosage form.

## ADANTAGES

**Improved Patient Compliance:** SR formulations reduce the frequency of dosing, often from multiple times a day to just once or twice. This makes it easier for patients to stick to their medication schedule[13].

**Enhanced Therapeutic Efficacy:** By maintaining steady drug levels, SR forms can reduce side effects that may occur from high peak concentrations and ensure the drug remains effective by preventing its concentration from dropping too low.

**Reduced Dosage Frequency:** A single SR dose can replace several smaller doses of a conventional drug, which is convenient for patients and caregivers.

### Matrix Tablets

Matrix tablets are a type of extended-release oral dosage form where the active and inactive ingredients are homogeneously dispersed in a three-dimensional network, or "matrix." This matrix controls the rate at which the drug is released into the body[14].

### The mechanism of drug release from matrix tablets

Drug release from matrix tablets is governed by a combination of dissolution-controlled and diffusion-controlled mechanisms, following Fick's first law of diffusion. Initially, drug particles on the tablet's surface dissolve and are released. Subsequently, gastrointestinal fluids penetrate the porous matrix, dissolving more drug particles. This dissolved drug then diffuses through the pores of the matrix to the exterior of the tablet. The rate of drug release is dependent on time and is defined by the following equation[15]:

$$Q/t^{1/2} = (2ACRD_p)^{1/2}$$

Where:

Q is the cumulative amount of drug released

t is time

A is the initial drug dose

CR is the drug reservoir concentration

D<sub>p</sub> is the diffusivity of the drug molecules in the polymer matrix

### Matrix tablets prepared

Matrix tablets can be prepared using one of the following methods[16]:

**Blending:** Finely ground drug particles are blended with a liquid or viscous polymer, followed by cross-linking of the polymer chains.

**Hot melt extrusion:** The drug and polymer are mixed at an elevated temperature.

**Solvent evaporation:** The drug and polymer are dissolved in a common solvent, which is then evaporated at an elevated temperature or under a vacuum.

### Types of matrix tablets

Matrix systems can be broadly categorized into three types[17]:

**Monolithic matrix tablets:** The drug is incorporated into an inert, non-interacting matrix. Drug release occurs via a leaching mechanism where gastrointestinal fluids penetrate the porous matrix, and the drug diffuses out. The tablet remains intact and does not disintegrate in the gastrointestinal tract.



**Gel-forming hydrophilic matrix tablets:** These tablets contain hydrophilic polymers that swell upon contact with water, forming a gel layer that controls drug diffusion.

**Erodible (hydrophobic) matrix tablets:** These tablets use hydrophobic materials that gradually erode or dissolve in the gastrointestinal tract, releasing the drug.

### Limitations of matrix systems

Some of the limitations of matrix systems include[18]:

**Lack of flexibility:** Adjusting to different dosage levels often requires a new formulation, which can be resource-intensive.

**Complex release profiles:** For products requiring unique release profiles (e.g., dual release or delayed plus extended release), more complex technologies like layered tablets are necessary.

**Poor direct compression characteristics:** Some inert polymeric matrices have poor direct compression characteristics, making their preparation challenging.

**Incomplete release:** At very low drug loadings, a fraction of the drug may be completely surrounded by the polymer matrix, leading to incomplete release.

**First-order drug release:** Many inert polymeric matrix tablets exhibit inherent first-order drug release characteristics, meaning the release rate is proportional to the amount of drug remaining, which may not be ideal for all applications.

### characteristics of drugs suitable for sustained-release oral dosage forms

For a drug to be a good candidate for a sustained-release formulation, it should possess the following characteristics[19]:

**Absorption and Excretion Rates:** The drug should have neither very slow nor very fast rates of absorption and excretion. Drugs with very short half-lives (less than 2 hours) are poor candidates due to the large quantities required, while drugs with long half-lives are already inherently long-acting.

**Uniform Gastrointestinal Absorption:** The drug must be uniformly absorbed from the gastrointestinal tract and have good aqueous solubility. Drugs with poor or unpredictable absorption are not suitable.

**Dose Size:** The drug should be administered in relatively small doses. Drugs requiring large single doses would result in a tablet or capsule that is too big for a patient to swallow easily.

**Safety Margin:** The drug should have a good margin of safety, also known as a high therapeutic index. Drugs with a narrow therapeutic index are poor candidates because of the risk of "dose dumping," where a large amount of the drug is released at once due to a product defect.

**Treatment Type:** The drug is typically used for chronic rather than acute conditions, as chronic conditions require less frequent dosage adjustments.

### Characteristics of drugs unsuitable for sustained-release dosage forms[20]

Based on the provided text, drugs with the following characteristics are unsuitable for sustained-release oral dosage forms:

Not effectively absorbed in the lower intestine (e.g., riboflavin, ferrous salts).

Absorbed and excreted rapidly, with short biological half-lives (less than 1 hour) (e.g., penicillin G, furosemide).

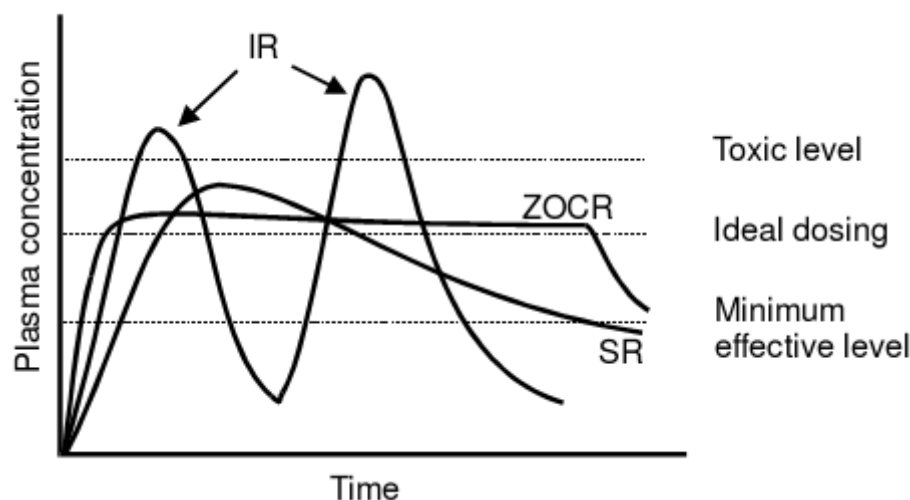
Long biological half-lives (greater than 12 hours) (e.g., diazepam, phenytoin).

Require large doses (greater than 1 gram) (e.g., sulfonamides).

Have cumulative action and undesirable side effects, or a low therapeutic index (e.g., phenobarbital, digitoxin).

Require a precise, individually titrated dosage (e.g., anticoagulants, cardiac glycosides).

Offer no clear advantage in a sustained-release formulation (e.g., griseofulvin).



characteristic representation of plasma concentrations of a conventional immediate release dosage form (IR), a sustained release dosage form (SR) and an idealized zero-order controlled release (ZOCR) dosage form (in combination with a start-up dose)[21]

### The different categories of polymers used in matrix tablets

The polymers used as drug-retarding agents in matrix tablets can be categorized into three main types[22]:

**Insoluble or skeleton matrices (plastic matrices):** These polymers are chemically inert and form an insoluble skeleton. Drug release is limited by liquid penetration into the matrix.

**Hydrophobic and water-insoluble materials:** These are potentially erodible materials (e.g., waxes) that control drug release through a combination of pore diffusion and erosion.

**Hydrophilic matrix systems:** These polymers, such as hydroxypropyl methylcellulose (HPMC), form a highly viscous, gelatinous surface barrier when exposed to an aqueous medium. This gel layer controls the release of the drug and the penetration of liquid into the core of the tablet. Hydrophilic matrices are the most widely used method for controlling drug release in oral pharmaceutical dosage forms.

### Biological Factors Influencing Extended-Release Drug Formulations

Extended-release drug formulations aim to maintain a steady concentration of a drug in the body over an extended period. However, several biological factors can significantly impact the effectiveness and feasibility of these formulations. These factors include absorption, distribution, and metabolism[23].

#### Absorption

Absorption is the process by which a drug enters the bloodstream. For an orally administered extended-release drug, its **rate of release** ( $K_r$ ) from the dosage form must be significantly slower than its **rate of absorption** ( $K_a$ ). [24] A crucial criterion for an effective formulation is  $K_r \ll K_a$ . If a drug has a very slow absorption rate

(e.g.,  $K_a < 0.17/\text{hr}$ ), it's difficult to formulate it into an extended-release system, as the release rate would need to be even slower, leading to poor bioavailability.

The following factors related to absorption can make extended-release formulations difficult:

**Erratic Absorption:** If a drug's absorption is inconsistent due to variations in the gastrointestinal tract, a sustained-release product will be hard to design. Examples include **Dicoumarol** and **Iron**.

**Active Transport Systems:** Drugs that rely on specific active transport mechanisms (e.g., amino acid or oligo-peptide transporters) for absorption are generally unsuitable for sustained-release delivery. This is because these transporters can become saturated, and the drug may not be absorbed effectively as it moves through the gastrointestinal tract. Examples include **Methotrexate**, **Enalapril**, **Gabapentin**, and **Cephalosporins**.

**Absorption Window:** Some drugs are only absorbed in a specific region of the gastrointestinal tract, known as an "absorption window." Once the extended-release formulation passes this window, the drug is no longer absorbed, leading to reduced bioavailability. This is a major obstacle for drugs like **Acyclovir**, **Captopril**, and **Metformin**.

**Local Action:** Drugs intended for a local therapeutic effect in the stomach, such as **antacids** or **Misoprostol**, are unsuitable for sustained-release systems, as their purpose is to act immediately in a specific area.

## DISTRIBUTION

Distribution describes how a drug spreads from the bloodstream to different tissues in the body. A key factor is the **apparent volume of distribution** ( $V_d$ ) [25].

**Large Volume of Distribution:** Drugs that have a large  $V_d$  are extensively bound to extravascular tissues (outside the blood vessels). For these drugs, the elimination half-life may be longer because the drug is gradually released from these tissues back into the blood. Such drugs, like **Chloroquine**, are considered **inherently sustained** and may not require a specific extended-release formulation.

## Metabolism

Metabolism is the process by which the body breaks down a drug. Complex metabolic patterns can make the design of an extended-release system more challenging [26].

**Enzyme Induction/Inhibition:** If a drug can either induce (speed up) or inhibit (slow down) the enzymes responsible for its own metabolism, it becomes difficult to maintain a uniform blood concentration, making it a poor candidate for a sustained-release product.

**First-Pass Effect:** If a drug is extensively metabolized in the gut wall or liver before reaching systemic circulation (the "first-pass effect"), a slow-release formulation can lead to a significant reduction in bioavailability. This is because the metabolic enzymes can become saturated, and the fraction of the drug lost would be dose-dependent. A drug with a variable first-pass effect is difficult to formulate into a sustained-release dosage form.

## Factors Affecting Drug Blood Levels and Sustained-Release Formulations

Several biological factors can cause fluctuating drug blood levels, making it difficult to design effective sustained-release (SR) or controlled-release (CR) formulations. These factors include:

## Metabolism

The metabolism of a drug can significantly impact its blood levels. The body metabolizes drugs in two main locations: the intestines and the liver [27].



**Intestinal and First-Pass Hepatic Metabolism:** When a drug is extensively metabolized in the intestines or liver before it reaches the bloodstream, this is known as the **first-pass effect**. This can lead to fluctuating drug levels and poor bioavailability. Examples of drugs with fluctuating blood levels due to intestinal metabolism include **Salicylamide** and **Isoproterenol**. Drugs affected by first-pass hepatic metabolism include **Morphine** and **Propranolol**.

**Enzyme Induction and Inhibition:** Some drugs can alter the activity of the enzymes that metabolize them.

**Enzyme induction** speeds up metabolism, causing drug levels to drop over time. Drugs like **Phenytoin** and **Rifampicin** are poor candidates for SR/CR formulations because of this.

**Enzyme inhibition** slows down metabolism, leading to a buildup of the drug. **Isoniazid** and **Cimetidine** are examples of drugs that inhibit enzymes and are therefore unsuitable for SR/CR systems.

### Dose-Dependent Bioavailability

For some drugs, the fraction of the dose that reaches systemic circulation changes with the dose itself. This makes it challenging to achieve consistent drug levels with a sustained-release formulation. **Propoxyphene** is a prime example; its bioavailability increases as the dose increases, making an SR/CR dosage form less desirable[28].

### Elimination Half-Life

The **elimination half-life** ( $t_{1/2}$ ) is the time it takes for the drug concentration in the body to be reduced by half. It is determined by the **volume of distribution** ( $V_d$ ) and **clearance** ( $Cl$ ), as shown by the formula[29]:

$$t_{1/2} = \frac{Cl}{0.693 \times V_d}$$

**Short Half-Life:** Drugs with very short half-lives (less than 2 hours) require a large dose to be incorporated into an SR/CR system, which may be impractical due to the size of the tablet or capsule.

**Long Half-Life:** Drugs with long half-lives (greater than 8 hours) are considered **inherently sustained**. They are already eliminated slowly from the body, so formulating them into an SR/CR product offers little to no therapeutic advantage over conventional dosage forms. Examples include **Meprobamate** and **Amitriptyline**. In some cases, like with corticosteroids, an SR formulation is undesirable as it can interfere with the body's natural diurnal rhythm.

### Mechanisms of Drug Release

Sustained-release formulations use various mechanisms to control drug release[30]:

**Diffusion:** The drug diffuses through a polymer matrix or a membrane. The rate of release is controlled by the thickness and permeability of this barrier.

**Dissolution:** The drug is encased in a slowly dissolving matrix or coating. The release rate depends on how quickly the matrix or coating dissolves.

**Erosion:** The drug is dispersed in a polymer matrix that slowly erodes in the body's fluids, releasing the drug as it breaks down.

**Osmosis:** An osmotic pump system uses water from the gastrointestinal tract to push the drug out of a semipermeable membrane at a controlled rate.

### DURATION OF ACTION

Duration of action is the time period for which the blood levels remain above the EMC and below the MSC levels (or) more specifically within the therapeutic window[31]. Drugs acting for long duration are unsuitable

candidates for formulation into SR/CR forms. Receptor occupation, Tissue binding, Half life, Metabolism, Partition coefficient, Irreversible binding to cells are some parameters which are responsible for long duration of actions of drugs[32].

## THERAPEUTIC INDEX

It is most widely used to measure the margin of safety of a drug[33].

$$TI = TD50 / ED50$$

The longer the value of TI the safer is the drug. Drugs with very small value of Therapeutic index are poor candidates for formulation into sustained release products. A drug is considered to be safe if its T.I value is greater than 101

## CONCLUSION

Sustained-release (SR) dosage forms are designed to release a drug slowly over an extended period. This provides a more consistent drug concentration in the bloodstream, avoiding the peaks and troughs associated with conventional, immediate-release medications. This approach offers several significant benefits for both patients and healthcare providers. It is helpful in increasing patient compliance and also improves efficiency in treatment. Certain criteria like molecular size, aqueous solubility must be met to incorporate the drug in sustained release dosage form. Sustained release dosage form undergo certain mechanisms for medicament release. Various pharmacokinetic and pharmacodynamic parameter should be taken under consideration before formulating a drug into sustained release dosage form.

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