REVIEW ARTICLE

Prolonged and Regulated Drug Delivery Mechanisms

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Received: 24th Aug, 2024; Revised: 25th Oct, 2024; Accepted: 27th Nov, 2024; Available Online: 25th Dec, 2024

ABSTRACT

Prolonged and regulated drug delivery mechanisms (PRDDM) have transformed pharmacotherapy by improving therapeutic effectiveness while reducing adverse effects. These advanced formulations are specifically designed to dispense active pharmaceutical ingredients at a controlled rate, ensuring a lasting therapeutic effect and maintaining drug levels within the optimal therapeutic range. Prolonged release mechanisms are developed to administer medication consistently over a prolonged duration, minimizing the need for frequent dosing and enhancing adherence to treat. On other hand, prolonged release mechanism (PRM) systems deliver a more accurate and consistent release profile, facilitating personalized drug administration according to individual patient requirements. To achieve PRDDM, various strategies are employed, including the incorporation of biodegradable polymers, hydrogels, and osmotic systems. The formulation elements can be customized to regulate drug release rates using processes like diffusion, breakdown/ osmotic. Additionally, progress in nanotechnology and 3D printing has opened new avenues for developing innovative drug delivery mechanisms.However, despite the many benefits, challenges like formulation stability, scalability manufacturing, and regulatory compliance remain significant issues that require attention. In summary, PRDDM signify notable progress in contemporary medicine, leading to better patient outcomes and enhanced therapeutic strategies. Ongoing research and innovation in this area are crucial to addressing current challenges and unlocking the full potential of cutting-edge drug delivery mechanisms.

Keywords: Prolonged Release, Regulated Release, Drug Delivery Mechanism, Pharmacotherapy and Biodegradable Polymers.

How to cite this article: Sravali G, Kumar CSP. Prolonged and Regulated Drug Delivery Mechanisms. International Journal of Drug Delivery Technology. 2024;14(4):2487-98. doi: 10.25258/ijddt.14.4.70

Source of support: Nil.

Conflict of interest: The authors affirm that they have no conflicts of interest to disclose.

INTRODUCTION

Traditional Drug Delivery Mechanisms

Traditional drug delivery mechanisms, often referred to as immediate -release formulations, represent the standard method for delivering medications. These systems quickly release the active pharmaceutical ingredient (API) once administered, resulting in a fast onset of therapeutic effects. They are commonly utilized in the treatment of various conditions, such as pain management, infection control, and cardiovascular diseases. Following are the examples

Paracetamol rapid onset Tablets

Paracetamol rapid onset tablets are designed for fast relief of pain and fever. They rapidly dissolve in GIT, leading to a quick raise in plasma concentration.[1]

Propranolol rapid onset Tablets

A beta-blocker used to manage hypertension and other cardiovascular conditions, propranolol rapid onset tablets provide quick therapeutic actions.[2]

Drawbacks of traditional drug delivery approach

Although traditional drug delivery approach are effective, they come with several limitations.[3]

Fluctuating plasma drug levels

The quick release of the drug can lead to fluctuation in plasma concentrations, causing high peaks that may result in side effects, while low troughs can lead to sub-optimal drug levels, reducing therapeutic effectiveness. Example: propranolol rapid onset tablets can cause fluctuations in blood pressure control, with peak levels potentially leading to hypotension and troughs level failing to deliver sufficient effect.

Short duration of action

many conventional formulations have a limited duration of action, requiring frequent dosing to sustain therapeutic levels. This can result in reduced patient adherence to the prescribed regimen. Example: levodopa rapid onset tablets, commonly used to manage parkinson's disease, need to be taken multiple times a day to control symptoms, which can be inconvenient for patients.

Increase side effects

The rapid release of the drug can lead to elevated initial plasma concentrations, raising the potential for side effects that vary with the administered dose. Example: Rapid onset nicardipine tablets, used for managing hypertension, may cause a sudden decrease in blood pressure, potentially resulting in dizziness or lightheadness.

Frequent Dosing Needed

Medications with short half-lives require multiple doses throughout the day, which can result in missed doses and inconsistent therapeutic outcomes. Example: Metformin rapid onset tablets, commonly prescribed for type 2 diabetes, typically require dosing two or thrice daily to sustain blood glucose regulation, which can impact adherence.

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Prolonged and regulated drug delivery mechanisms (PRDDM)

Prolonged and regulated drug delivery mechanisms (PRDDM) were designed to overcome the limitations of traditional formulations. These advances systems are formulated to release the active pharmaceutical ingredient (API) at a steady state, ensuring stable plasma concentration over a prolonged periods.[4,5,6]

Sustained release (SR)

SR are formulated to release the API gradually, prolonging its therapeutics effect and reducing the need for frequent dosing. By controlling the release rate, SR system help maintain consistent drug levels in the bloodstream. Example: Diclofenac sustained -release tablets, commonly used to treat chronic pain and inflammation, offer extended relief by releasing the drug over a period of 12 to 24 hours, thereby reducing the need for multiple doses throughout the day.

Controlled release (CR)

Controlled release deliver is formulated to release the active ingredient at consistent, predefined rate, and ensuring stable plasma levels maintained at therapeutic window. This precise regulations improves both the efficacy and safety of the treatment. Example**:** Propranolol controlled-release capsules are designed for once-daily dosing,gradually releasing the drug over 24 hours .This ensures consistent blood pressure management while reducing the likelihood of side effects.

How prolonged and regulated drug delivery mechanisms overcome conventional system's limitation?

Paracetamol sustained Release Tablets

Unlike rapid onset dosage forms, paracetamol sustained release offers prolonged pain relief with just a single dose, reducing the frequency of administration and minimizing fluctuations in plasma levels.

Propranolol Controller-Release capsules

The capsules address the limitations of rapid onset formulations by ensuring stable blood pressure control throughout the day, minimizing the risk of flactuations that could cause side effects or reduce treatment effectiveness.

Definitions in Modified Release Drug Delivery systems

Various definitions for are as follows[7,8]

Extended Release (ER)

ER systems formulated to release the API gradually over time,extending the duration of action compared to rapid onset versions. Examples: Metaprolol extended-release tablets, used to treat hypertenions, offer once-daily dosing by gradually releasing for a 24-hour period.

Delayed Release (DR)

DR systems releases the API at a predetermined time post-administration, typically activated by variation in pH or enzymatic activity in the gastrointestinal tract. Example: Omeprazole delayed-release capsules, used to treat gastroeosophageal reflux disease (GERD), release the API in the enteron rather than the gasteron, protecting it from degradation by gastric acid.

Repeat Action

These are formulated to provide an initial dose of the drug, followed by additional doses released at specific intervals, ensuring sustained therapeutic levels over a prolonged duration. Example: Chlopheniramine maleate repeat-action tablets, used for allergy relief, offer immediate symptom relief followed by a secondary release of the drug several hour later.

Targeted Release

These are formulated to deliver the API directly to or close to the intended site of action, minimizing systemic exposure and lowering the likelihood of side effects. Example: 5-fluorouracil targeted release systems in cnacer therpay deliver the drug directly to tumor tissues, minimizing toxicity to healthy cells.

Merits and demerits of prolonged and regulated drug delivery mechanisms

The merits and demerits were as follows[9,10]

Merits

Improved patient compliance

Lower dosing frequency improves patients adherence to the medication regimen. Example:Glipizide extended-release tablets, used in managing diabetes, are taken once daily,simplifying adherence to the treatment plan for patients.

Stable plasma drug levels

These systems deliver a more consistent therapeutic effects by maintaining steady drug concentrations,thereby reducing side effects linked to peak levels. Example: Theophylline sustained-release capsules provide steady bronchodilation for asthma patients by preventing the fluctuations in drug levels seen with rapid onset formulations.

Reducing in side effects

These systems reduce the likelihood of dose dependent adverse reactions by avoiding excessively high peak plasma levels. Example: Verapamil controlled release tablets provides consistent blood pressure control while reducing the risk of hypotension or bradycardia, in contrast to rapid onset formulations.

Enhanced therapeutic effect

Prolonged action ensures continuous symptom control, leading to better overall treatment outcomes. Example: Nifedipine extended-release tablets, used to treat angina and hypertension, offer continuous vasodilation and consistent blood pressure control.

Demerits

Complex and Costly manufacturing

The development and production of Prolonged and regulated drug delivery mechanisms are more complex and costly compared to conventional formulations. Example: Controlled-release morphine tablets, used for chronic pain management, require advanced manufacturing processes, which make them more expensive than rapid onset morphine formulation.

Risk of uncontrolled drug release

Failure of the release mechanism can result in the unintended rapid release of the entire drug dose, potentially causing toxicity. For instance, damage to the coating of controlled release verapamil tablet could lead to accelerate drug release.

Individual variability

Table 1: Differences between traditional drug delivery approaches and Prolonged and regulated drug delivery mechanisms.[11,12]

Features	Traditional Drug delivery	Prolonged and regulated drug delivery mechanisms
Drug release profile	Rapid release, immediate action	Slow, controlled or prolonged release
Plasma drug concentration	Peaks and troughs fluctuating levels	Stable, consistent levels
Dosing frequency	Multiple doses per day	Reduced frequency, once or twice daily
Side effects	Higher risk due to peak concentrations	Lower risk due to controlled levels.
Patient compliance	Lower due to frequent dosing	Higher due to frequent dosing
Manufacturing complexity	Simple and less costly	More complex and expensive
Risk of dose dumping	Low	Potential risk if system fails
Adaptability to physiological changes	Moderate varies with formulations.	May be affected by individual physiological factor.

Physiological differences among patients, such as variation in gastrointestinal pH or motility, can influence the drug release profile, potentially leading to inconsistent therapeutic outcomes. Example: phenytoin extended-release capsules, used in the treatment of epilepsy, may exhibit variable absorption in patients with different gastrointestinal conditions, potentially affecting drug level.

Limited dose flexibility

Unlike rapid onset formulations, adjusting the dose of SR or CR formulations is more complex, which limits flexibility in dose titrations. Example: Metaprolol extended-release tablets offer fewer options for dose adjustments when compared to rapid onset tablets, which can be split or combined to achieve varying doses**.**

Differences between traditional drug delivery approaches and Prolonged and regulated drug delivery mechanisms (As showed in Table 1)

Approaches to PRDDMS

Prolonged release drug delivery mechanisms are engineered to administer medication steadily for a prolonged duration, managing consistent therapeutic concentration while reducing unwanted effects. Several strategies have been developed to achieve these goals, each with its own unique mechanisms, advantages, and applications. Below are detailed notes on the primary approaches used in Prolonged and Regulated Drug Delivery Mechanisms, along with relevant examples.[13,14]

Mechanisms governed by diffusion

Diffusion controlled systems enable sustained and controlled API release by regulating its movement through a polymeric membrane or matrix, which determines the release rate.

Polymeric matrix mechanisms

API is uniformly dispersed within a polymer, which may be porous or non-porous in nature. The release of the drug occurs as it diffuses from the matrix, facilitating a regulated and prolonged release over an extended duration.

Matrix systems-Types

Homogeneous matrix mechanisms

The drug is uniformly distributed within polymer matrix, which release occurring as the molecules slowly diffuse out. For example, Theophylline SR tablets use water soluble polymer matrix, like hydroxypropyl methyl cellulose (HPMC), to control gradual release of the drug for a prolonged period.

Heterogenous matrix mechanisms

API will be embedded in matrix containing both soluble and insoluble components. The soluble components dissolve initially, forming pores that allow drug to permeate gradually through matrix. Example**:** Propranolol extended release tablet dosage forms utilize a heterogeneous matrix system made of methacrylate copolymers, which helps extend the gradual release of the API.

Reservoir mechanisms

In reservoir systems, the drug is housed within a polymeric membrane that controls the rate of active ingredient release. The release rate is primarily influenced by the membrane's permeability and the drug's solubility. Example: nitroglycerine transdermal patches use a reservoir mechanism, in which the API contained in a membrane that controls its release onto the skin over a 24 -hour period.

Solubility-Regulated mechanisms

These mechanisms operate through the dissolution of either the active ingredient or the polymer matrix that contains it. These dissolving rate of drug or polymer directly assesses overall release rate of the API.[15,16]

Encapsulation dissolution systems

In these mechanisms, the API encapsulated within a polymer coating that gradually dissolves in gastrointestinal fluids, allowing the drug to be release over time. Example: Verapamil controlled-release capsules use a polymer coating of ethyl cellulose, which dissolves at a controlled rate, ensuring the API releases gradually over a prolonged duration.

Matrix dissolution mechanisms

The API incorporated within a matrix made of a material that gradually dissolves in body fluids. As the matrix dissolves, the drug is progressively released. Example: Carbamazepine extended-release tablets use a matrix dissolution system, where the polymer matrix, such as HPMC, gradually dissolves, permitting the medication to be dispensed gradually over a prolonged duration

Mechanisms regulated by osmotic pressure

These mechanisms utilizes the osmotic pressure for controlled release of API, these systems typically comprise an API core surrounded by semipermeable membrane. Water from gastrointestinal fluids passes through the membrane, generating osmotic pressure that drives the API out through a small opening at a consistent and controlled rate.[17,18]

Key features

Semipermeable membrane

The membrane allows water to enter but prevents the drug from diffusing out,ensuring prolonged release mechanism through the system.

Osmotic agents

These compounds frequently incorporated into the core to increase osmotic pressure, facilitating a steady and controlled delivery of the drug.

Orifice

A small aperture within the membrane facilitates the controlled delivery of the active components, driven by osmotic pressure within the system. Example: Glucotrol XL, an extended release formulation of glipizide, utilizes osmotic pressure to regulate API release, providing consistent therapeutic effect for 24 hours.

Erosion-controlled systems

Erosion-controlled systems work by the gradual degradation or erosion of a polymer matrix, delivering the active component as the matrix collapse over time. These systems are especially effective for delivering drugs that require slow release over and extended period.[19,20]

Types of erosion-controlled systems

Surface erosion systems

The polymer matrix erodes from the surface inward,gradually releasing the API as the outer layer break down. Example:Gliadel wafer (carmustine implant), used in the treatment of brain cancer, is designed to erode at a steady rate, delivering the chemotherapy API directly to the tumor site over an extended period.

Bulk erosion systems

The entire polymer matrix erodes uniformly, resulting in an accelerated release of active component once erosion process reaches a specific stage. Example: Zoladex (goserelin acetate implant) utilizes biodegradable polylactic acid-glycolic acid (PLGA) polymer that undergoes bulk erosion, allowing for prolonged release mechanisms of the drug over several months.

Ion exchange resin mechanisms

Thee mechanisms function through the reversible interaction of ions between the API and the resin. The API is attached to the resin, and upon exposure to GI fluids, ions in the fluid replace the API on the resin, enabling its controlled release.[21,22]

Mechanism of action

The API is releases as it is exchanged with ions in the gastrointestinal tract. The release rate can be regulated by properties of resin and ionic strength of surrounding fluids. Example: Tussionex pennkinetic extended-release suspension (hydocodone and chloropheniramine) uses an ion exchange resin to extend the release of the cough suppressant and antihistamine, enabling less frequent dosing.

Expansion regulated release mechanisms

These mechanisms use polymers that expand upon contact with bodily fluids, resulting in a prolonged release mechanism of API. The controlled expansion of polymer structure determines the rate at which API disperses.[23,34]

Swelling rate

Rate at which the polymer swells determines speed of API release. The active ingredient is released either by migrating through the expanded polymer structure or via the degradation of the polymer material. Example: Hydrogel-based delivery system, such as naltrexone implants, use swelling-prolonged release mechanism. In these systems, the hydrogel swells upon contact with water, gradually releasing the drug over extended periods.

Site specific therapeutic delivery platforms

These therapeutic delivery platforms are designed to transport the medication directly to a particular area within the body, minimizing systemic exposure and enhancing therapeutic outcomes at the intended site. Depending on their design, these systems may also incorporate mechanisms for sustained or extended drug release.[25,26]

Approaches to targeted delivery

Ligand-targeted systems

These systems utilize ligands attached to the drug carrier that specifically bind to receptors on the targeted cells, ensuring targeted delivery of the drug. Example: Herceptin (transtuzumab) is conjugated with cytotoxic agents to specifically target HER-2 positive breast cancer cells, delivering the drug directly to the cancer cells.

Nanoparticle-based systems

These systems encapsulated APIs and designed to release them stimuli responsive, like variations in pH or temperature, or precisely target specific tissues. Example: Doxil (liposomal doxorubicin) targets tumor cells more effectively than conventional doxorubicin, improving efficacy while reducing side effects.

Gastro-retentive systems

Gastro-retentive system are designed to extend the residence time of active component in the gasteron, enabling prolonged delivery mechanism of active component throughout GIT. These mechanisms are specifically beneficial to active components, that exist as most effectively taken up in stomach or upper part of the enteron.[27,28]

Types of gastro-retentive systems

Floating systems

These systems float on gastric fluids, ensuring prolonged retention in the stomach and providing sustained drug release over an extended period. Example: Ciproflaxacin floating tablets offer prolonged gastric retention and prolonged release mechanisms of the antibiotic, enhancing its bio availability.

Mucoadhesive system

Such formulations adhere to the gastric mucosa, increasing their residence time and facilitating sustained delivery of active ingredients. Example**:** Mucoadhesive tablets of verapamil adhere to the stomach lining, allowing for prolonged drug release and improved management of hypertension.

Pulsatile release systems

Pulsatile release mechanisms are formulated to deliver the active component pulses at predetermined intervals. This method is especially beneficial for drugs that need to follow a specific dosing schedule to align with the body's natural rhythms or for conditions that benefit from intermittent drug release.[29,30]

Types of pulsatile systems

Time-controlled systems

These systems delivers the active component following a predetermined delay (lag time), mimicking the body's natural circardian rhythms. Example: The pulsincap system for diltiazem is designed to release the drug during the early morning hours, when blood pressure typically rises, thereby enhancing the management of hypertension.

Stimuli-responsive systems

These systems activate the release of the active component via physiological stimuli responsive, such as change in pH, temperature/ enzyme levels. Example:Insulin pumps that deliver insulin in response to glucose levels are a form of stimuli-responsive pulsatile delivery, administering insulin only when needed to maintain optimal blood sugar levels.

Microencapsulation and nanoencapsulation systems.

Microencapsulation and nanoencapsulation involve enclosing the drug in micro or nanoparticle to achieve controlled or prolonged release mechanisms. These systems protect the drug from degradation and regulates its release rate through diffusion or erosion mechanisms.[31,32]

Microencapsulation

Micro encapsulation involves enclosing the drug within a polymeric shell that control its release over time**.** Example: Ritalin LA (methylphenidate extended-release capsule) use microencapsulation to enable a biphasic delivery of the active component, with an initial discharge followed by prolonged release mechanisms over several hours.

Nanoencapsulation

Nanoencapsulation offers even greater control over drug release, often used for targeting specific tissues or permeating bio-barriers, such as the BBB. Example**:** Abraxane (paclitaxel protein-bound particle) uses nanoencapsulation to enhance the delivery and efficacy of paclitaxel in cancer treatment, enabling ontrolled release while reducing toxicity.

Transdermal delivery systems

A transdermal system (TDS) offers a non-invasive approach for delivering medication in gradual and regulated way through skin. TDS deliver medication consistently over extended duration, often lasting several days, thereby enhancing patient adherence.[33,34]

Mechanism of action

The medication is delivered through a patch that adheres to the skin. The release rate is regulated by permeation of medication through adhesive layer and skin, ensuring a steady flow of medication over time. Example: Fentanyl transdermal patches provide prolonged release mechanisms of the opioid analgesic over 72 hours,delivering consistent pain relief for patients with chronic pain condition.

Evaluation of PRDDMS

The evaluation of prolonged and regulated drug delivery mechanisms is essential to ensure these drug delivery systems achieve the desired therapeutic effects while maintaining safety and efficacy. The evaluation process involves various tests and analyses to assess parameters such as drug release profiles, stability, bioavailability, pharmacokinetics, and overall performance of the formulation. Below are detailed notes on the evaluation of Prolonged and Regulated Drug Delivery Mechanisms, along with relevant examples.

***In vitro* evaluation**

In vitro evaluation includes testing the medication release from the sustained or prolonged release mechanism system under controlled laboratory conditions. This assessment offers critical understanding of the system's drug release dynamics, rate of delivery, and potential *in vivo* performance.[35,36]

Dissolution testing

Purpose

The purpose of dissolution testing is to assess the speed and quality of drug discharge from the formulation, offering insights into its release profile over time under standardized conditions.

Methods

USP apparatus 1 (basket) and 2 (paddle)

These serves as widely used dissolution apparatuses where medication is introduced into dissolution fluid, and the medication release is tracked over a period.

Apparatus 3 (reciprocating cylinder)

These apparatus are used for formulations that require testing in different media, stimulating the pH variations of gastrointestinal tract to assess how drug release may be affected under physiological conditions.

Parameters assessed

Dissolution profile

It is the speed and pattern of drug released from formulation into dissolution medium over time. It provides essential information about the drug's release kinetics and helps predicts its behaviour in the body. Example: The dissolution testing of metformin extended-release tablets involves placing the tablet in a dissolution medium and Quantifying the metformin discharged within 24 hours verifies that the medication is delivered consistently in alignment with the intended release pattern.

Drug release kinetics

Purpose

To analyze how the drug is discharged from formulation, providing insights into whether diffusion, erosion, swelling, or other pathways are involved and how these mechanism influence the overall release pattern.[37,38]

Models used

Zero order profile

In zero-order profile, the API delivered at uniform rate that does not depend on its concentration within the formulation. This allows for a consistent release pattern over time, ensuring a controlled and predictable therapeutic outcome.

First order profile

In first-order profile, the drug release rate depends on remaining quantity of the drug within formulation, decreasing proportionally as the drug depleted. As drug is released, release rate gradually declines over time, indicating a process dependent on concentration.

Higuchi model

The Higuchi model describes drug release from matrix system as diffusion controlled process proportional to the square root of time.This mechanism, rooted in Fickian diffusion principles, highlights that the drug release rate depends on time's square root. This model is widely applied

to the solid dosage forms where diffusion dominates the release process.

Korsmeyer-Peppas model

This model is widely employed to determine the drug release mechanism, which may involve Fickian diffusion, non-Fickian transport, or Case II (zero-order) release. Analysis of release data using the release exponent (n) helps identify the dominant release pattern from the matrix system:

Fickian diffusion ($n < 0.5$): Drug release is controlled by diffusion.

Anomalous transport ($0.5 < n < 1$): A combination of diffusion and polymer relaxation influences the release

Case II transport ($n = 1$): Polymer swelling or erosion dominates and resulting in a zero-order release profile

This phenomenon is less common than Fickian diffusion or standard Case II transport but is critical in understanding complex drug delivery system involving highly dynamic matrices. Example:Nifedipine extended-release tablets are evaluated using these model to determine that drug adheres zero-order, indicating a steady drug release over time, which ensured steady plasma concentration and consistent therapeutic effects.

Swelling studies

Purpose

This parameter helps determine how the matrix absorbs water and swells over time, which in turn affects the drugs release rate. In hydrophilic matrix systems, swelling plays a crucial role in regulating the drug release rate from the formulation. Monitoring degree of swelling, formulators can optimize the release profile and ensure consistent drug delivery.

Method

Formulation is dropped in a dissolution fluid, and degree of swelling measured by calculating the increase in weight or the change in dimension of the matrix over time. This allows for the assessment of how the matrix expands and interacts with the surrounding fluids, providing insights into the release mechanism and helping to predicts the drug's release profile.[39,40] Example:HPMC-based theophylline sustained-release tablets undergo swelling studies to evaluate how the polymer matrix swells overtime. This swelling behavior influences the drug release rate, as increasing volume of matrix affects diffusion of drug. By monitoring extent and pattern of swelling, formulators can better understand and control release characteristics of the formulation.

Erosion studies

Purpose

To evaluate the erosion rate of polymeric matrices in erosion-prolonged release mechanism systems, the formulation is typically placed in a dissolution medium, and the weight loss or changes in the matrix structure are measured overtime.[41]

Method

The weight loss of the formulation is measured over time in a dissolution medium to determine the erosion rate. Drug release occurs as the polymer matrix degrades, with weight loss indicating the breakdown of the material. This helps assess how the erosion process influences the prolonged release mechanisms of the drug. Example: Poly (lactic-co-glycolic acid) (PLGA) - based implants subjected to erosion studies to understand how the polymer degrades over time, controlling release of the encapsulated drug. By measuring the weight loss and changes in the implant's structure in a dissolution medium, formulators can determine how the erosion process impacts the rate and duration of drug release from the implants.

***In vivo* evaluation**

In vivo evaluations involves testing the sustained or prolonged release mechanism systems in a living organism (such as animal models or humans) to asses the system's pharmacokinetic (PK) and pharmacodynamic (PD) behavior. This evaluation is essential to confirm that the system perform as expected in the physiological environment, ensuring that drug is released at the desired rate, achieves therapeutic levels, and produces the intended pharmacological effect.[42,43]

Pharmacokinetic studies

Purpose

In vivo assessments are conducted to evaluate the absorption, distribution, metabolism, and excretion (ADME) of a drug from sustained or prolonged release system. These studies provide insight into how the drug enters the bloodstream, its distribution within the body, the metabolic processes it undergoes, and its elimination pathway.

Parameters assessed

C_{max} (Maximum plasma concentration)

The peak plasma concentration of drug in bloodstreams is referred to as C_{max}. it represents highest concentration of drug achieved after administration, indicating how quickly the drug is absorbed and how much is available for therapeutic action at a given time.

T_{max}(time to reach C_{max})

The time required to reach C_{max} is known as T_{max}, represents the moment when drug concentration in the blood stream peaks after administration. This pharmacokinetic parameter is crucial for evaluating the absorption rate of drugs, particularly in sustained or prolonged release formulations.

AUC (Area under the curve)

It represents the overall drug exposure over time, serving as a critical pharmacokinetic parameter. It is determined by plotting plasma drug concentration against time and calculating the area beneath the curve. A higher AUC signifies increased drug exposure, aiding in evaluating the effectiveness and bioavailability of sustained or prolonged release system.

Half-life ($t_{1/2}$)

It is the duration needed for the drug's plasma concentration to decrease by 50%. It is vital pharmacokinetic measure that indicates the time required for body to remove half of administered dose. Example: Fentanyl transdermal patches are evaualted through pharmacokinetics studies to ensure that they provide consistent plasma level of fentanyl over 72 hours, maintaining a steadt drug concentrations and avoiding the peak and troughs typically seen with convenionals dosing methods. These studies help confirm that the patch delivers the drug at controlled rate, ensuring

effective pain management without casuing sudden fluctuations in blood levels or side effects.

Bioavailability studies

Purpose

Bioequivalence studies are conducted to assess the bioavailability of drug from sustained systems compared to first acting formulations or reference standards. These studies compare pharmacokinetic parameters like C_{max}, T_{max}, AUC, and $t_{1/2}$ to evaluate drug absorption rates. The objective is to confirm that sustained release systems offer similar therapeutic outcomes and drug exposure as immediate release formulations, with advantages such as reduced dosing frequency and enhanced patient compliance.[44]

Method

Plasma concentration-time profiles are generated and analyzed to evaluate the absorption rate and extent of drug release from sustained or extended systems. By tracking drug levels in the systemic circulation over time, researchers can assess important pharmacokinetic parameters like C_{max}, T_{max}, AUC, and $t_{1/2}$. These profile helps determine how quickly the drug is absorbed, how long it stays in bloodstream, and whether the prolonged release mechanism formulation delivers the drug at the desired rate and extent compared to an rapid onset or reference standard. Example: Osmotic-prolonged release mechanism oral delivery system(OROS) for methylphenidate are evaluated for bioavailability, demonstrating that the system provides a similar extent of absorption as the rapid onset formulation but with a more prolonged release mechanism pattern. The OROS system releases the drug steadily over time, maintaining therapeutics level of methylphenidate throughout the day, thereby reducing the need for multiple doses and minimizing the fluctuations in plasma drug concentrations typically seen with rapid onset formulations.

Pharmacodynamic studies

Purpose

To assess the therapeutic effect of the drug released from Prolonged and Regulated Drug Delivery Mechanisms, clinical efficacy studies are conducted. These studies evaluate how well the drug maintains its therapeutic action over time, ensuring that the prolonged release mechanism system provides consistent and effective drug level for the desired therapeutic outcome.[45]

Method

The pharmacodynamic response (eg. Reduction in blood pressure, pain relief) is measured and correlated with the drug release and pharmacokinetics profile to assess the therapeutic effectiveness of sustained and prolonged release mechanism system. By monitoring clinical outcomes and comparing them with plasma concentration-time profiles, researchers can determine whether the drug's therapeutic effect align with the prolonged release mechanism of the drug. Example: Controlled-release nifedipine formulations are assessed for their capacity to provide stable blood pressure management over a 24 hour period, offering prolonged therapeutic effects white avoiding the fluctuations typically observed with rapid onset versions.

Toxicological studies

Purpose

The safety of the sustained or controlled-release system is assessed,with a focus on identifying any potential toxicity related to extended drug exposure.[46]

Method

Animal models are employed to evaluate the long term effects, and the results are used to estimate potential safety outcomes in humans. Example: Long-acting injectable antipyschotics undergo toxicological testing to confirm that the drug does not build up to harmful levels in the body with prolonged use.

Stability studies

Stability studies are performed to verify that the sustained or controlled-release system retains its efficacy, safety, and quality throughout its shelf life.[47,48,49]

Accelerated stability testing

Purpose

To assess the formulation's long term stability, it is stored under accelerated conditions, such as elevated temperature and humidity, for a short duration.

Parameters assessed

Physical stability

Evaluation of alterations in the appearance, hardness, or structural integrity of the dosage form.

Chemical stability

Examining drug breakdown products and tracking the maintenance of its effectiveness.

Microbiological stability

Ensuring the formulation stays free from microbial contamination. Example:Accelerated stability testing is conducted on controlled-release formulations of atenolol to confirm that they preserve their release profile and potency over time.

Long-term stability testing

Purpose

To verify the formulation's stability under recommended storage conditions throughout its intended shelf life.

Method

The formulation is stored under standard conditions, with periodic testing performed to evaluate its stability. Example: Long-term stability testing is conducted on sustained-release formulations of metformin to ensure they retain consistent release profiles and efficacy throughout their shelf life.

***In vitro - in vivo* correlation (IVIVC)**

IVIVC is an analytical framework that links *in vitro* properties, such as dissolution rate, to *in vivo* outcomes, like plasma drug concentrations. Developing a reliable IVIVC is vital for the designed and refinement of sustained or controlled release formulations.[50,51]

levels of IVIVC

Level A

A direct relationship between *in vitro* dissolution and *in vivo* absorption.

Level B

A relationship between the average *in vitro* dissolution time and the average *in vivo* residence time.

Level C

Single point interconnection between a specific *in vitro* dissolution time and a pharmacokinetic parameter (eg.$C_{max,}$AUC). Example**:** Extended-release formulation of

venlafaxine are assessed using Level A IVIVC, enabling estimates of *in vivo* drug release behaviors dependent on *in vitro* dissolution profile.

Clinical evaluation

Clinical evaluation involves testing the sustained or prolonged release mechanism system in human subjects to assess its safety, efficacy and overall performance in the target population. This step is essential before the product can be approved for marketing.[52,53,54]

Phase 1 Clinical Trails

Purpose

This exploratory clinical investigation aimed to scrutinize the harmless, acceptability, and bioavailability profiles of the novel compound in a compact ensemble of asymptomatic individuals.

Focus

Determining the correct dosage and understanding the release characteristics of the formulation in humans. Example: Phase 1 trials for a extended release systems of an antihypertensive drug assess its safety and release profile in healthy volunteers.

Phase 2 clinical trials

Purpose

This pivotal clinical trail sought to assess the therapeutic potency and risk benefit profile of the investigational product in an expansive cohort of subjects affliated with the specified clinical entity.

Focus

Optimizing the dosage and confirming the sustained pr controlled-release characteristics in the patient population. Example: phase 2 trails of a controlled-release analgesic formulation evaluate the drug's ability to provide consistent pain relief.

Phase 3 clinical trails

Purpose

This definitive clinical validation study aimed to corroborate the therapeutic effectiveness and harmlessness of the novel formulation in a substantial patient demographic, while concurrently juxtaposing its clinical outcomes with those of established therapeutic paradigms.

Focus

Establishing the sustained or controlled-release formulations as a viable treatment option. Example: Phase 3 trials of a controlled-release formulation of an antidepressant confirm its efficacy in providing stable mood control over 24 hours, with fewer side effects compared to rapid onset formulations.

Post marketing surveillance [phase 4]

Purpose

This post marketing surveillance initiative aimed to scrutinize the prolonged tolerability and therapeutic durability of formulation amidst diverse real world patient cohorts subsequent to regulatory sanction.

Focus

Detecting uncommon or latent sequelae that may manifest in response to prolonged exposure, and ensuring that sustained or controlled-release system continues to perform as expected. Example: Post-marketing surveillance of a sustained-release anti-diabetic drug helps monitor its long-term safety in diabetic patients, ensuring it does not lead to unexpected hypoglcaemia. Sustained and controlled drug delivery systems have significantly advanced pharmaceutical formulations by providing a steady release of drugs, improving therapeutic outcomes, and enhancing patient compliance. These systems are engineered to deliver therapeutic agent at steady rate, delivering prolonged therapeutic effects while reducing effects reducing side effects. Below are detailed applications of sustained and controlled drug delivery systems, along with relevant examples for each

Applications of PRMDDS

The following are the application of PRDDM drug delivery systems[55-74]

Chronic Disease Management

Cardiovascular Diseases

PRDDM play a pivotal role in managing cardio-circulatory disorders, including elevated blood pressure, thoracic angina, and cardiac insufficiency. By facilitating consistent pharmacokinetic profiles, these systems mitigate the necessity for repetitive administrations, thereby augmenting adherence to therapeutic regimens exposure. Example: verapamil hydrochloride Extended-release tablets are used to manage hypertension and angina. The prolonged release mechanism of verapamil provides steady blood pressure control throughout the day, allowing for convenient once-daily dosing.

Diabetes

Managing diabetes typically involves maintaining stable blood glucose levels. Sustained-release formulations help achieve prolonged therapeutic effects, minimizing the risk of both hypoglycemia and hyperglcemia. Glipizide extended-release tablets offer controlled blood glucose management for type 2 diabetes patients, reducing the need for frequent dosing and helping to minimize fluctuations in blood sugar levels**.**

Pain Management

Chronic pain

Sustained and controlled-release systems play a essential role for managing chronic pain conditions such as arthritis, cancer pain, and neuropathy. By delivering consistent pain relief over an extended period, these systems help enhance patients' quality of life. Example: Morphine sulfate Extended-Release tablets provide prolonged pain relief for patients with chronic pain, minimizing dosing frequency and sustaining a consistent pain-relief plateau across a 24-hour cycle.

Post-surgical pain

Controlled-release formulations are commonly used in post-operative care to manage pain effectively, this refers to advantages of innovative pain management formulations designed to combat opioid abuse. Example: Oxycodone Extended-Release Tablets are used to manage severe post-surgical pain, providing up to 12 hours of relief with a single dose.

Neurological Disorders

Epilepsy

Sustaining steady state pharmacokinetics is crucial in epilepsy treatment to avert paroxysmal episodes. Controlled-release formulations help achieve steady-state plasma concentrations, reducing both the frequency and

severity of seizures. Example: Carbamazepine controlled-release Tablets aid in managing epilepsy by maintaining consistent drug levels, thereby reducing the risk of breakthrough seizures.

Parkinson's Disease

Sustained-release formulations in parkinson's disease help maintain steady dopaminergic activity, reducing motor fluctuations and enhancing patient mobility. Example: Levodopa/Carbidopa Controlled-Release Tablets are used to provide steady symptomatic relief for parkinson's patients, minimizing the "on-off" phenomenon and improving overall motor control.

Oncology

Cancer Treatment

Controlled-release systems are used to administer chemotherapy drugs at a controlled rate helping to reduces systemic toxicity and enhance the benefit to risk ratio of the pharmacological agent.

Hormone Therapy

Sustained-release systems are commonly used in hormone therapy for cancer patients to maintain stable hormone levels and minimize the need for frequent doses. Example: Goserelin Acetate Implants are used to manage prostate cancer, It delivers steady release of the hormone analog over a period of months, decreasing the frequency of required injections.

Respiratory Diseases

Asthma

Sustained-release formulations are employed to ensure consistent bronchodilation in asthma patients, helping to reduce the frequency of flare-ups and enhance lung function. Example: Theophylline sustained-release tablets aid in asthma management by offering extended bronchodilation, which reduces the need for frequent dosing.

Chronic Obstructive Pulmonary Diseases (COPD)

Controlled-release systems are effective in managing COPD by ensuring stable drug levels, alleviating symptoms, and enhancing patient adherence to treatment. Example: For instance, Tiotropium Bromide Inhaler with sustained-release formulations are used in the long-term management of COPD, offering 24-hour bronchodilation with a single daily dose.

Gastrointestinal Disorders

Inflammatory Bowel Disease (IBD)

Sustained-release systems are employed to target drugs directly to the site of inflammation in inflammatory bowel disease (IBD), minimizing systemic side effects and enhancing treatment effectiveness. Examples: Mesalamine controlled capsules are used to treat ulcerative colitis and crohn's disease by releasing drug directly in colon, reducing systemic absorption and ensuring targeted treatment.

Gastrointestinal Reflux Disease (GERD)

Sustained- release formulations used in the management of GERD help maintain consistent inhibition of gastric acid production, alleviating symptoms and enhancing patient comfort. Example: Omeprazole Delayed-Release capsule offer prolonged acid suppression, helping to decrease both the frequency and intensity of GERD symptoms.

Infectious Diseases

HIV /AIDS

Controlled-release systems are used in the management of HIV infection to maintain stable levels of antiretroviral drugs, reduce the need for frequent dosing, and enhance patient adherence to treatment. Example: Tenofovir Alafenamide/Emticitabine Sustained-Released formulations assist in managing HIV by delivering extended viral suppression with a single daily dose.

Tuberculosis

Sustained-release formulations are utilized in tuberculosis treatment to ensure steady drug concentrations, minimizing the risk of resistance and enhancing overall treatment effectiveness**.** Example: Rifampicin sustained-release capsules deliver extended antibacterial activity, helping to improve patient compliance and increase treatment success rates.

Hormonal Disorders

Diabetes (Insulin Therapy)

Controlled-release systems are employed to deliver insulin steadily, closely resembling body's natural insulin release and enhancing blood glucose regulation. Example: Insulin Glargine (long -acting insulin) offers 24-hour basal insulin coverage, minimizing the need for multiple daily injections and helping to maintain stable blood glucose levels.

Contraception

Sustained-release systems are employed in contraceptive methods to offer long-term birth control, reducing the need for daily pill intake and improving adherence to the regimen. Example: The levonorgestrel Intrauterine Device (IUD) gradually release levonorgestrel over several years, providing reliable contraception with minimal user involvement.

Ophthalmic Applications

Glaucoma

Sustained-release systems are utilized in glaucoma management to maintain stable intraocular pressure, helping to reduce the risk of optic nerve damage. Example: Timolol maleate Ophthalmic gels are used to provide sustained intraocular pressure reduction in glaucoma patients, ensuring consistent drug levels while minimizing the frequency of dosing.

Post-Surgical Care

Controlled-release formulations are used in post-surgical opthalmic care to deliver extended anti-inflammatory and analgesics effects, promoting healing and improving patient comfort. Example: Dexamethasone Intravitreal Implants are used following cataract surgery to deliver prolonged anti-inflammatory effects, reducing the need for frequent eye drop applications.

Dermatological Applications

Psoriasis

Sustained- release topical formulations are designed to maintain steady drug levels in the skin, decreasing the frequency of application and enhancing patient adherence to the treatment regimen. Example: Calcipotriol/ Betamethasone Dipropionate sustained-release ointment is used to treat Psoriasis, offering extended relief with just a once-daily application**.**

Acne

Controlled-release formulations are employed in acne treatment to deliver prolonged antibacterial and anti-inflammatory effects, minimizing the need for frequent applications. Example: Clindamycin/ Benzoyl Peroxide Controlled-Release Gel is used in acne treatment to ensure steady drug delivery over several hours, helping to reduce the risk of skin irritation.

CONCLUSION

The design, optimization, and formulation of PRDDM play a crucial role in achieving therapeutic objectives by ensuring the controlled release of APIs, tailored to meet patient specific needs. These system have been effectively utilized to treat a various conditions by accommodating APIs with diverse physicochemical and pharmacokinetic properties. By aligning the choice of PRDDM with specific characteristic of API, these systems have been successfully employed across numerous therapeutic applications. Despite certain limitations, PRDDM remain pivotal in the pharmaceutical landscape, owing to their capacity to augment pharmacological potency, foster adherence, and elevated holistic treatment efficacy. This review aim to explore the significance and versatility of PRDDMs, providing insights into their design, applications, and potential for addressing complex medical needs.

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