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Review Article

EXTENDED RELEASE DRUG DELIVERY: BALANCING PHARMACOKINETICS, PATIENT COMPLIANCE, CURRENT PERSPECTIVES AND ADVANCEMENTS IN EXTENDED-RELEASE TABLETS

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ABSTRACT
Extended-release (ER) drug delivery systems have become a critical breakthrough in pharmaceutical sciences in response to difficulties related to typical immediate-release drugs. ER systems improve therapeutic activity, provide plasma drug levels consistently, decrease frequency of dosing, and increase patient compliance. There are many types of ER formulations including matrix systems, diffusional controlled delivery, dissolution controlled systems, osmotic pumps, and ion-exchange resins. In vivo testing is crucial for the purpose of determining the pharmacokinetic parameters of ER products and retaining bioavailability, therapeutic efficacy, and patient safety for the end user. Pharmacokinetic studies such as Cmax, Tmax, and AUC indicate absorption, and distribution of drug. Bioavailability and bioequivalence studies also confirm therapeutic equivalence to reference products. Advanced imaging techniques such as gamma scintigraphy and in vivo-in vitro correlation (IVIVC) models establish drug release properties. Emerging developments in ER preparations are directed toward biodegradable polymers, stimuli-sensitive hydrogels, nanocarriers based on nanotechnology, and predictive modeling based on artificial intelligence. Such developments target improvements in controlled release of drugs, reduction of side effects, and maximization of patient benefit. Nevertheless, these challenges as aspects of formulation challenges, regulatory implications, and financial considerations remain pivotal areas of investigation and development.

KEYWORDS: Extended-release, drug delivery system, pharmacokinetics, matrix tablet, controlled release, polymer technology.

INTRODUCTION

The term oral drug delivery is used to describe the administration of a dosage form orally for local effect or systemic absorption along the gastrointestinal (GI) tract. Oral drug delivery has been the most commonly used route of administration for decades because it is noninvasive, convenient, pain avoidance and has high patient compliance. It does not need any special sterile conditions. The conventional drug delivery systems have been marked with immediate release and frequent dosing of the medication, which could result in the risk of fluctuation in doses hence, there arises a need for formulation with controlled release in blood. Hence, in today's world, most pharmaceutical scientists are engaged in designing an ideal DDS. This system of a deal must be benefited with the advantage of a single dose throughout the period of treatment, and it must administer the drug at a single site in a controlled way.[1][2]

Modified release drug delivery systems are innovative drug forms that allow to control over the rate and location of medication which release in the body. They have various advantages over traditional dose forms, such as increased therapeutic efficacy and less side effects. Modified release systems can enable prolonged, delayed, or regulated medication delivery by altering the physicochemical characteristics of the drug and the carrier. Common techniques include matrix systems, reservoir systems, and stimuli-responsive systems. In matrix systems, the drug is embedded in a polymer matrix and in reservoir systems, the drug is enclosed within a rate-controlling membrane. Stimuli-responsive systems release the medicine when subjected to pH, temperature, or enzymes.[3]

Advantages of Modified Release Drug Delivery System

1. Enhanced control over drug maintenance of therapeutic plasma drug concentration.
2. Enhanced patient compliance, brought about by the fewer number and less frequent dosing to sustain the desired therapeutic effect.
3. Enhanced of duration of action for short half life drugs.
4. Improved bioavailability of some drugs.
5. Minimize drug accumulation with chronic dosing.

Disadvantages of Modified Release Drug Delivery System

1) Slow release of drug may produce a localized concentration that causes local irritation to gastrointestinal mucosa.
2) Drugs having biological half lives of 1 hour or less are difficult to formulate modified release. The high rates of elimination of such drugs from the body mean that an extremely large maintenance dose would be required to provide 8-10 hours continuous therapy.
3) When the formulation is not well planned, there is a risk of sudden release of the entire drug dose (dose dumping) and subsequent toxicity and side effects.
4) Requires advances skills and technology to prepare formulations, resulting in expense and complication versus typical drug formulation.
5) Certain drugs must be metabolized quickly or undergo first-pass activation and are not suited to modified-release preparations.[4]

Modified Release Drug Delivery Systems Can Be Divided Into The Following Categories

1. Delayed released
2. Controlled released
3. Sustained released
4. Extended released
5. Site specific released
6. Receptor targeting

1. Delayed Released Drug Delivery System

These systems are based on pH dependent drug release mechanism of similar to conventional enteric-coated formulations but they differ in target site for delivery and therefore type of enteric polymers. Most commonly used polymers for preparation of delayed release system are derivatives of acrylic acid and cellulose. These polymers have the capability to endure low pH conditions for several hours.

Example: Enteric coated tablets, capsules which includes repeat action tablets, achieve time-controlled release through a protective barrier coating.

2. Controlled Released

These systems maintain constant level of drug in blood and tissue for extended period of time. It implies predictability and reproducibility in drug release kinetics. An ideal controlled drug delivery system is the one, which delivers the drugs at a predetermined rate locally or systematically for a specific period of time optimizing therapeutic efficacy while reducing side effects.

3. Sustained Released

These systems achieves slow and steady release of drug over an extended period of time after administration of single dose.

4. Extended Released

Extended release drug delivery system is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

5. Site-Specific And Receptor Targeting

In the case of site-specific release, the target is a certain organ or tissue, while for receptor release, the target is the particular receptor for a drug within an organ or tissue.[5]

Extended Released Drug Delivery System

Extended-release (ER) tablets are designed to gradually release their active pharmaceutical ingredient over a extended period of time, this can increase the therapeutic effect. This can improve patient compliance by lowering dose frequency and increasing therapeutic efficacy by keeping more constant medication levels in the blood circulation. This means this is specifically used for the longer duration of action of dosage forms up to 6-12 hrs. And it can be extended up to 24 hours of the therapeutic effect. In this type of dosage form the release of the API can control up to the desired time.

Matrix tablets are considered to be the commercially feasible extended action dosage forms that involve the least processing variables, utilize conventional facilities, and accommodate large doses of the drug. There remains an interest in developing novel formulations that allow for extended drug release using readily available, inexpensive excipients by matrix-based formulation.[6]

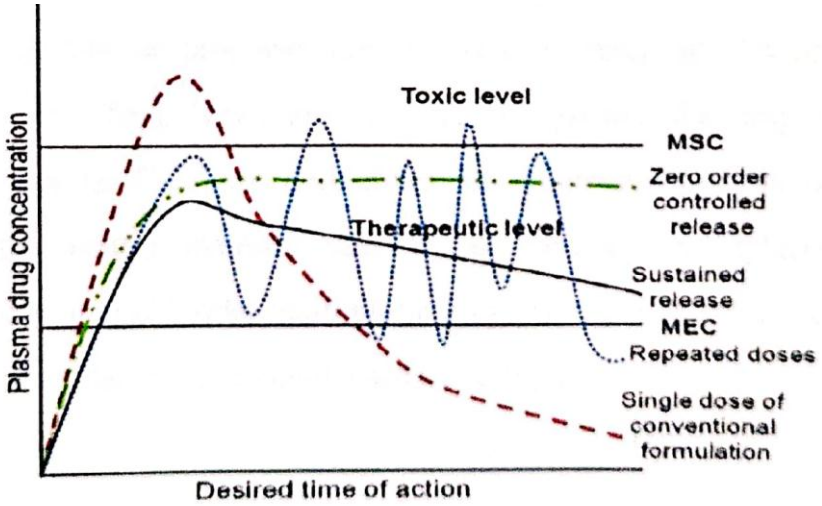

Figure: A hypothetical plasma drug concentration – time profile from conventional multiple and single doses of sustained and extended delivery formulation

Advantages of Extended-Release Matrix Tablet

1. Reduce dosage frequency.
2. Reduce fluctuation in circulating drug levels.
3. Increase patient compliance.
4. Avoidance of nighttime dosing.
5. More uniform effect.
6. Reduction in GI irritation and dose-related side effects.
7. Improvement of treatment efficacy.
8. Usage of less total drug.

Disadvantages of Extended-Release Matrix Tablet

1. Highly expensive.
2. Often poor systemic availability.
3. Need for additional patient education and counseling.
4. Dose dumping.
5. Often poor invivo–invitro correlation.[7]

Types Of Extended Release Formulations

Many current oral extended release systems are available

1. Diffusion-controlled release system.
2. Dissolution-controlled release system.
3. Dissolution and diffusion controlled release system.
4. Ion exchange resin-drug complex.
5. Slow dissolving salts and complexes.
6. pH- dependent formulation.
7. Osmotic pump system.

1. Diffusion-Controlled Release System

Diffusion-controlled release systems are drug delivery techniques that regulate and prolong the release of active medicinal ingredients by utilizing the diffusion process. In this method, a medication moves from an area of higher concentration within the dosage form to a region of lower concentration in the biological environment surrounding the dosage form across a rate-limiting barrier, such as a polymer membrane or matrix.

Fick's rules of diffusion govern the release rate.

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

where

D = is the diffusion coefficient in area/time

C = is the concentration,

X = is the distance.

This law states that the drug diffuses in the direction of decreasing concentration.

These systems are categorized mainly into two types:

- Reservoir devices
- Matrix device systems

A. Reservoir Devices

In a reservoir devices the diffusion occurs in a thin film surrounding the release unit. The drug release occurs by diffusion through the membrane. The release rate is typically zero-order in reservoir devices meaning it remains constant over time. This constant release is facilitated by a concentration gradient between the drug inside the core and the surrounding fluid. In this system, a drug core is covered in a water-insoluble polymeric substance. The drug will partition into the membrane and interact with the fluid surrounding the particle or tablet. Additional medication will pass through the membrane, diffuse to the periphery, and interact with the surrounding medium.

B. Matrix Devices

In matrix systems, the drug is embedded within a porous matrix. Initially, drugs near the surface dissolve and are released quickly. As the process continues, the drug deeper within the matrix dissolves and diffuses through the pores to the exterior of the release unit. The drug release follows a diffusion process that is dependent on the concentration gradient.

2. Dissolution-Controlled Release Systems

In this system the rate of drug dissolution in gastrointestinal (GI) juices or other surrounding mediums controls the release of the drug. These systems are

especially helpful for drugs that are sparingly soluble in water, as they can create preparations where the dissolution rate becomes the rate-limiting step of drug release.

One of the standard techniques to obtain dissolution-controlled extended release is through coating the drug particles with a slowly dissolving barrier. The drug release from such units follows a two-step mechanism:

1. Coating Dissolution: The coating first dissolves in the liquid surrounding the release unit, which usually constitutes the controlling step in the release process.

2. Drug Dissolution: Once the coating is dissolved, the drug is introduced to the liquid in contact with it and dissolves within the medium.

For some of the slowly dissolving drugs, the dissolution process itself tends to cause extended release. These drugs lend themselves naturally to this kind of system. Examples of such drugs are digoxin, griseofulvin, and salicylamide. These drugs have a naturally slow dissolution rate, and when prepared in dissolution-controlled systems, they get released slowly.

When the drug is very water-soluble and has a high rate of dissolution, a way of sustaining release is by reducing the drug's solubility. This is done through the formation of suitable derivatives or salts of the drug. Yet, it has its disadvantages because it may not always be possible to achieve a consistent availability rate since the surface area of the drug becomes less over time due to the dissolving action.

3. Dissolution And Diffusion Controlled Release System

This approach involves encasing the drug core in a partly soluble membrane. Pores are formed as a result of membrane breakdown, which allows aqueous medium to enter the drug core, and therefore drug dissolution allows dissolved drug to diffuse out of the system. An example of producing such a coating is utilizing a combination of ethyl cellulose with PVP or methyl cellulose, which dissolves in water and forms holes in the insoluble ethyl cellulose membrane.

4. Ion Exchange Resin-Drug Complex

Controlled release of ionizable acidic and basic drugs can be achieved by combining them with insoluble, non-toxic anion and cation exchange resins. In this system, the drug is gradually released through diffusion from within the resin matrix. The following equation illustrates the release mechanism of a basic drug (NH_2R) from a cation exchange resin (RSO_3H) when it comes into contact with gastrointestinal (GI) fluid containing an ionic compound (A^+B^-), such as gastric HCl or intestinal NaCl.

$$RSO^-_3NH_3^+R + A^+B^- \longrightarrow RSO^-_3\,A^+ + NH_3^+R\,B^-$$

Basic drugs like noscapine, phenylpropanolamine and phentermine have been retarded by such an approach.

5. Slow Dissolving Salts And Complexes

Drug salts and complexes that dissolve slowly in GI fluids can be utilized to regulate the release of API. Amine medicines can react with tannic acid to produce poorly soluble complexes that can be packaged into long-acting tablets. Penicillin G has been complexed with N, N-dibenzyl ethylenediamine to produce benzathine penicillin G, which may be administered as an oral solution. Such complexes can be formed by combining separate component solutions by a simple acid-base reaction.

6. Ph- Dependent Formulation

These systems are intended to reduce the effect of gastrointestinal pH differences on medication disintegration and absorption. This is accomplished by include suitable levels of buffering agents (such as phosphoric, citric, or tartaric acid salts), which keep the pH stable as the dose form passes through the GIT. This guarantees constant medication solubility and release rates, regardless of stomach pH. The drug-buffer combination is encased in a permeable covering that permits aqueous medium penetration but prevents tablet dispersion.

7. Osmotically Controlled Drug Release

In these systems, medication release is regulated by the entry of water across a semipermeable membrane into a reservoir holding an osmotic agent known as osmogens. This results in a consistent and carefully regulated medication release, with generally constant blood concentrations. One advantage of this approach is that medication release is unaffected by the gastrointestinal environment, relying exclusively on water penetration into the dosage form. The release rate can be modified by changing the osmotic agent or the size of the delivery aperture.[8]

Polymers Used In Extended Release Tablets

The most commonly used polymers for the preparation of matrix systems include both hydrophilic as well as hydrophobic polymers:[9]

a) Hydrophilic polymers

- Xanthan gum
- Sodium Alginate
- poly (ethylene oxide)
- cross-linked homopolymers and co-polymers of acrylic acid
- Hydroxyl propyl methyl cellulose (HPMC)
- Hydroxyl propyl cellulose (HPC)
- Hydroxyl ethyl cellulose (HEC)

b) Hydrophobic polymers

This typically consists of waxes and water-insoluble polymers in its composition.

c) Natural polymers

- Sodium Alginate
- Pectin
- Chitosan

● Xanthan Gum
● Guar Gum

d) Biodegradable polymers
● Polycaprolactone (PCL)
● Polyanhydrides
● Polyorthoesters
● Polylactic acid (PLA)
● Polyglycolic acid (PGA)

e) Non-biodegradable polymers
● Polyvinyl chloride (PVC)
● Cellulose acetate (CA)
● Ethyl cellulose (EC)
● Polyethylene vinyl acetate (PVA)
● Polydimethylsiloxane (PDS)
● Polyether urethane (PEU)

Factors affecting the extended release drug Delivery system

A. Physiochemical Properties of the drug

1. Aqueous Solubility

In order for a drug to be absorbed in the body, it must dissolve in GI fluids. The drugs of low solubility may not fully dissolve over GI transit time, and therefore their bioavailability decreases. Conversely, drugs with very high solubility are also undesirable for ER formulations since it is hard to control their release. The drug of choice for ER formulations should possess moderate solubility that is pH-independent.

2. Partition Coefficient

Since biological membranes are largely lipophilic, drug passage is regulated by the lipid solubility of a drug. A drug with very poor solubility in lipids becomes trapped in the aqueous phase and achieves minimal absorption. Extremely lipophilic drugs become trapped in cell membranes and fail to release properly. Thus, an optimum range of the partition coefficient is necessary so that both the absorption and release will be equally balanced.

3. Drug Stability in the Body

For a drug to be suitable for an ER formulation, it must remain stable in the GI tract. When it degrades in acidic pH or through enzymes, its bioavailability is lost, and thus ER formulations are unsuccessful. For example, nitroglycerin and penicillins degrade in the stomach, and thus other forms of delivery like patches or injections are required.

4. Protein Binding

Most of drugs are bound to plasma proteins and only the free fraction is active. Highly protein-bound drugs will naturally have extended durations of action and thus ER forms are not needed. Moderately protein-bound drugs are more amenable to ER systems because their controlled release can provide constant blood levels.

5. **pKa & Ionization at Physiological pH**

A drug's absorption depends on its ionization state at body pH levels. Only the non-ionized (neutral) form of a drug can pass through membranes easily. Drugs that remain mostly ionized in the GI tract are poorly absorbed and unsuitable for ER formulations. The ideal pKa range for ER drugs is 3.0–7.5 for acids and 7.0–11.0 for bases.

6. Absorption Mechanism & Site

Drugs absorbed exclusively in particular GI segments or need specialized transporters (e.g., B vitamins) are not appropriate for ER formulations. On the other hand, drugs absorbed by passive diffusion along the entire GI tract are the best candidates.

7. Molecular Size & Diffusivity

Lower-molecular-weight drug molecules (<500 Da) have greater permeability through biological membranes and are ideal for ER products. Large molecules are difficult to absorb, particularly when their diffusion depends on polymers.

8. Size of the dose

Large dose drugs (>500 mg) are challenging to the ER formulations, as they make the tablet or capsule too bulky and difficult to produce and swallow. Smaller doses are better suited to convenient ER drug design.

B. Biological Properties of Drug

1. Absorption

- For ER drugs, the rate of absorption (ka) must be much greater than the release rate (kr) (i.e., kr <<< ka).
- Poorly absorbed drugs or drugs with variable absorption are not suitable for ER formulations.
- Low absorption can be caused by poor solubility, low partition coefficient, acid hydrolysis, metabolism, or site-specific absorption.

2. Distribution

- High Vd drugs are eliminated quickly and not suitable for ER systems (e.g., Chloroquine).

3. Metabolism

- Extensively metabolized drugs (e.g., Levodopa, Nitroglycerin) are unsuitable for ER since steady plasma levels cannot be maintained.

4. Half-Life of Drug

- Ideal half-life for ER dosage form: 2–8 hours.
- Half-life < 2 hours → ER is impracticable because it requires high dosing.
- Half-life > 8 hours → There is no need for ER formulation.

5. Margin of Safety

- Narrow therapeutic index drugs are not ideal for ER formulations since small changes may cause toxicity so therapeutics index of drugs should be broad.

6. Plasma Concentration-Response Relationship

- Drugs whose effects depend on plasma concentration are suitable for ER.
- Drugs with activity independent of plasma levels (e.g., Reserpine) are not good candidates for ER formulations.

Drug Selection For Oral Extended-Release Drug Delivery System

The biopharmaceutical evaluation of a drug for potential use in a controlled release drug delivery system requires knowledge of the absorption mechanism of the drug from the G.I. Tract, the general absorbability, the drug's molecular weight, solubility at different pH, and apparent partition coefficient.

1. Physicochemical Parameters for Drug Selection

The biopharmaceutical attributes of a drug decide whether it is appropriate for controlled release formulations or not. These are absorption properties, solubility, molecular weight, and partition coefficient.

Table No. 1: Physicochemical Parameters for Drug Selection.

Sr. No.	Parameters	Preferred-Value
1.	Molecular weight/ size	500 Daltons
2.	Solubility	> 0.1mg/ml for pH 1 to pH 7.8
3.	Apparent partition coefficient	High
4.	Absorption mechanism	Diffusion
5.	General Absorbability	From all GI segments
6.	Release	Should not be influenced by pH and enzymes

2. Pharmacokinetic Parameters for Drug Selection

Knowledge of a drug's pharmacokinetics is essential in devising an ER system that delivers constant blood concentrations over a sustained period. Parameters to consider here are half-life, rate of clearance, bioavailability, and therapeutic concentration.[10]

Table No. 2: Pharmacokinetic parameters for drug selection.

Sr. No.	Parameters	Preferred-Value
1.	Elimination Half-life	Preferably between 2 and 8 hrs
2.	Total clearance	Should not be dose-dependent
3.	Elimination rate constant	Required for design
4.	Absolute Bioavailability	Should be 75% or more
5.	Intrinsic absorption rate	Must be greater than the release rate
6.	Therapeutic concentration Css av	The lower Css av and smaller V_d, the loss among of drug required
7.	Toxic concentration	Apart from the values of MTC and MEC, safer the dosage form is also suitable for drugs with very short half-lives.
8.	Apparent volume of distribution V_d	The larger the V_d and MEC, the larger will be the required dose size.

Methods Of Preparation Of ER Formulation

There are 3 methods of preparation of extended release tablets.

Direct Compression

In direct compression, finely powdered materials are directly mixed and compressed in tablets without adding any granulating liquid or water. Those API are moisture or heat sensitive and if we want to prepare tablets this direct compression is the best option.

Wet Granulation

In this method, firstly weighted quantities of drug and polymer are mixed with sufficient volume of granulating agent or water. After enough cohesiveness was obtained, the mass is sieved and dried at suffient temperature. Then lubricants and glidents are added and tablets are compressed using tablet compression machine.

Melt Granulation

Melt granulation is a solventand binder-free technique used in producing extended-release (ER) tablets. In the melt granulation process, a bindermaterial of a known melt temperature (such as polyethylene glycol (PEG) or waxes) is heated until it melts and acts as a binding agent that fuses powder particles together into a granule. These granules serve as the tablet cores. Once cooled, the solidified binder forms a matrix, which controls the release of the drug primarily through diffusion and/or erosion mechanisms.[11]

List of various drugs which can be formulated as extended release matrix tablet with polymer and its method used to prepare

DRUGS	CATEGORY	METHOD USED	POLYMER USED
Salbutamol Sulphate	Bronchodilator	Direct Compression	Locust Bean Gum, HPMC K15M[12]
Zidovudine	Antiretroviral (HIV/AIDS)	Wet Granulation	Eudragit RLPO, RSPO, Ethyl Cellulose[13]
Enalapril Maleate	Antihypertensive (ACE Inhibitor)	Wet Granulation	HPMC K4M, HPMC K15M[14]
Oxybutynin Chloride	Anticholinergic (Overactive Bladder)	Direct Compression	HPMC K4M, HPMC K100M, Carbopol, PVP, Ethylcellulose, Sodium Alginate[15]
Glipizide	Antidiabetic (Sulfonylurea)	Wet Granulation	HPMC K100M, Eudragit L100[16]
Norfloxacin	Antibiotic (Fluoroquinolone)	Direct Compression	HPMC, Polyethylene Oxides (PEOs)[17]
Diltiazem	Calcium Channel Blocker	Direct Compression	HPMC 643, Povidone[18]
Desvenlafaxine	Antidepressant	Wet Granulation	Methocel K15M, Sodium Alginate[19]
Tramadol HCl	Opioid Analgesic	Wet Granulation	Eudragit RS-100, Ethylcellulose, Carbopol 934P, PVP K-90[20]
Stavudine	Antiretroviral (HIV/AIDS)	Wet Granulation	HPMC K4M, Carbopol 974P[21]
Verapamil HCl	Calcium Channel Blocker	Solid Dispersion, Direct Compression	HPMC K4M, Poloxamer 188[22]
Losartan Potassium	Antihypertensive (ARB)	Direct Compression	Eudragit RLPO, RSPO, Ethyl Cellulose[23]
Theophylline	Bronchodilator	Wet Granulation	HPMC K4M, HPMC K100M, Eudragit, Chitosan[24]
Metformin HCL	Antidiabetic	Wet Granulation	Eudragit RSPO, Gum Copal, Gum Damar[25]
Metoprolol Succinate	Antihypertensive (Beta-blocker)	Direct Compression	HPMC K4M, K15M, K100M, PEO 303[25]
Venlafaxine HCl	Antidepressant	Direct Compression	HPMC E4M, E15LV, E50LV, Eudragit L100[26]
Propranolol HCl	Antidysrhythmics	Wet granulation	native dextran, hydrochloride hydroxypropyl methylcellulose (HPMC)[27]
Lamivudine	Antiviral	Direct compression	Methocel K15M CR[28]

Current Perspectives and Advancements in Extended-Release Tablets

Longer-acting, extended-release (ER) tablets keep pace with improvements in formulation sciences and materials technology. Latest trends focus on drug release kinetics precision using innovation such as 3D printing for tailoring dosages to individual requirements and multi-layer matrices for optimizing dual-phase drug release profiles. Emerging polymers such as lipid-based nanoparticles, polyesters with aster-like groups in their directly-connected 2nd carbon, dual stimuli-responsive hydrogels, and lipid nanocarriers aim to enhance biocompatibility and bioavailability for controlled delivery. Moreover, implementing AI and ML for obtaining predictive models regarding behavior of the formulation releases has significantly reduced time-consuming iterative refinements of design optimization through trial and error. Sustainability is also an emerging trend, with studies on green excipients and solvent-free methods such as hot-melt extrusion (HME) to reduce environmental footprints. Patient-friendly designs are becoming a greater emphasis in the field, e.g., orally disintegrating ER tablets or microbead-based formulations for pediatric and geriatric patients. Improved "smart" ER systems, which react to physiological stimuli (e.g., pH, enzymes, or temperature), are designed to maximize therapeutic effects for complicated conditions such as diabetes or cancer. There remains, however, a challenge in meeting cost-effectiveness with sophisticated manufacturing methods and regulatory compliance for new delivery systems.

Academic and industrial collaborations and regulatory agility on the part of novel platforms are leading the second-generation ER tablets toward precision therapy and worldwide reach.

CONCLUSION

The potential to take over therapeutics in a variety of medicines through the stringent drug discrimination, rational formulation optimization as well as advanced technology. modulation of drug release, improved bioavailability, and superior patient compliance, especially in chronic regimens. ER tables have a more effective, safe and patient compliant pharmaceutical treatments. They also offer an advantage with regard to rational The preparation of sustained release delivery systems is still the key elements toward.

Future trends in the field will probably face formulation and regulatory challenges, and seek to progress to more intelligent, responsive, and eco-friendly drug delivery systems. Strong research collaboration between academia, industry, and regulatory organizations is required to bring new and innovative ER systems to market in a timely manner that match the greater patient needs around the world.

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