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RECENT ADVANCES IN CONTROLLED AND SUSTAINED RELEASE DRUG DELIVERY SYSTEM: A SYSTEMATIC REVIEW

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Abstract

Modern biopharmaceutics has been significantly reshaped by the evolution of controlled and sustained drug delivery systems, which optimize therapeutic outcomes, cut down on dosing frequency, limit systemic side effects, and boost patient adherence. Progress in nanotechnology, smart biomaterials, and polymer engineering has greatly broadened the scope of these advanced formulation platforms. Today, novel carriers-including polymeric nanoparticles, liposomes, dendrimers, hydrogels, micelles, nanocrystals, exosomes, and metal– organic frameworks-offer superior drug targeting, better bioavailability, and precise site-specific release profiles. Furthermore, smart stimuli-responsive networks triggered by internal or external factors like pH, temperature, enzymes, ultrasound, magnetic fields, or light allow for exact spatio-temporal control over when and where the drug payload is liberated. While sustained release formulations focus primarily on prolonging the temporal availability of a drug through modified first-order kinetics, true controlled release systems target structural and physiological parameters to achieve precise, zero-order release profiles. This systematic review comprehensively evaluates the structural configurations, functional classification, and recent breakthroughs in these delivery designs. Together, these ongoing clinical innovations pave the way for highly tailored, efficient, and patient-centric treatments, providing promising opportunities across diverse medical fields, particularly in cancer chemotherapy, cardiovascular disorders, infectious diseases, and regenerative medicine.

INTRODUCTION

The historical timeline of pharmaceutical development has been defined by a constant effort to optimize how therapeutic compounds enter and move within the human body. Clinically active molecules, or active pharmaceutical ingredients cannot achieve their true therapeutic potential without an efficient transport vehicle. For generations, conventional dosage forms such as

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standard oral tablets, capsules, and simple liquid injections served as the foundation of medical treatments. While these traditional formulations successfully managed acute and chronic conditions, they suffered from significant biopharmaceutical limitations. Traditional immediate release systems lead to an unpredictable "peak-and-valley" fluctuation of drug concentrations in the bloodstream, often spiking into toxic ranges before dropping below the minimum effective concentration. This erratic behavior requires patients to take multiple doses throughout the day, which lowers patient compliance and increases systemic toxicity. To resolve these challenges, modern pharmaceutical research has introduced advanced drug delivery technologies designed to deliver medication in a manner that selectively increases drug concentration in targeted body regions relative to others [1]. Historically, the concept of modifying drug release began mid-twentieth century with simple macro-encapsulation techniques, but it has evolved into a highly sophisticated field driven by nanotechnology and macromolecular chemistry. Within this domain, controlled drug delivery refers to systems where the release of the active agent from the bulk structural matrix is deliberately engineered and mathematically predictable. Although the academic literature frequently uses "controlled release" and "sustained release" interchangeably, they are distinct mechanisms.

Sustained release denotes a formulation engineered to deliver a drug over a prolonged duration, attempting to mimic zero-order kinetics through a slow, first-order controlled release mechanism. Conversely, true controlled release systems specifically manipulate molecular structures and physiological variables to achieve strict zero order kinetics, ensuring a constant drug release rate that is entirely independent of the remaining drug concentration. Advanced drug delivery platforms can be broadly classified based on their underlying release mechanisms and physical composition. These include diffusion-controlled matrix systems, dissolution-controlled reservoirs, chemically triggered bio erodible frameworks, and swelling-controlled hydrogels. In diffusion systems, the active compound is physically trapped inside a polymer network, moving outward down a concentration gradient. Dissolution networks rely on the steady, calculated breakdown of an outer barrier coat. Swelling systems, or responsive hydrogels, absorb biological fluids upon administration, expanding their polymer chains to allow the trapped therapeutic payload to escape.

This is achieved by altering the pharmacokinetics or pharmacodynamics of active moieties, either through innovative delivery architectures or by modifying molecular structures and physiological variables [2]. An ideal drug delivery platform must possess specific physical, chemical, and biological characteristics to ensure clinical success. Biocompatibility and non-toxicity are baseline requirements; the carrier material must degrade into harmless, non-immunogenic metabolites that the body can easily eliminate. Additionally, the system must maintain structural stability during storage, shield its active payload from chemical breakdown, and release the drug at a highly reproducible, predictable rate without causing a sudden "burst release" effect. The vehicle must also possess adequate mechanical strength to withstand physiological pressures while remaining flexible enough to navigate vascular pathways. The constituents and materials used to build these modern platforms are diverse, bridging the gap between natural biology and synthetic engineering. Polymeric nanoparticles, liposomes, dendrimers, micelles, and nanocrystals have emerged as leading nano-carriers capable of encapsulating both hydrophilic and lipophilic compounds. Naturally derived exosomes and bio-engineered metal–organic frameworks offer advanced ways to bypass cellular membranes.

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Concurrently, smart stimuli-responsive systems have grown rapidly.

These systems act as intelligent networks activated by internal biological triggers-such as altered pH levels in tumor microenvironments or specific localized enzymes or external physical stimuli like temperature shifts, ultrasound waves, magnetic fields, or light, enabling precise control over drug release. The practical applications of these advanced systems are extensive, reshaping critical sectors of modern healthcare. In oncology, targeted nano-carriers deliver highly toxic chemotherapeutic drugs directly to tumor masses via the enhanced permeability and retention effect, sparing healthy tissues from severe side effects. In cardiovascular medicine, drug-eluting stents and localized micro-particles release anti-restenotic compounds directly inside damaged arteries to prevent blockages. For infectious diseases, sustained formulations provide a continuous, long-term supply of antibiotics or antivirals, preventing the emergence of drug-resistant pathogens due to missed doses. Finally, in regenerative medicine and tissue engineering, bio-compatible hydrogels serve as structural scaffolds that release growth factors in a highly regulated sequence, guiding cellular migration and accelerating tissue repair. Ultimately, the overriding objective of any advanced delivery platform is to prolong, confine, and target the therapeutic agent within diseased tissues while ensuring protective interactions.

Controlled release system

A controlled release configuration represents an advanced drug delivery platform specifically engineered to liberate a predetermined quantity of a therapeutic agent over a designated, predictable timeframe. The mechanical objective of this design is to establish and maintain a constant, unfluctuating concentration of the active compound within the systemic circulation. By doing so, it effectively minimizes adverse side effects while reducing the overall dosing frequency required for effective management [4]. Expanding on this concept, Robinson and Lee define controlled release drug delivery as the strategic integration of specialized formulations, manufacturing technologies, and delivery architectures designed to precisely govern the rate, temporal sequence, and specific anatomical location of drug liberation within the biological system. The ultimate goal of this approach is to successfully meet clinical objectives while mitigating systemic toxicity [5]. Consequently, these sophisticated architectures are meticulously designed to sustain optimal plasma drug concentrations within the desired therapeutic window for prolonged durations [6].

Sustained release system

On the other hand, sustained release drug delivery frameworks represent distinct dosage forms engineered to liberate their therapeutic payload in a gradual, incremental manner over a prolonged operational timeline. The primary focus of a sustained release network is to ensure that the concentration of the active medication circulating in the bloodstream or localized tissues remains therapeutically effective for an extended period [8]. By maintaining a steady state of drug availability and avoiding sharp drops in plasma levels, sustained release configurations substantially decrease the frequency of drug administration. This continuous therapeutic coverage not only optimizes clinical outcomes but also significantly enhances patient adherence and long-term compliance [9].

Characteristics of sustained release system

The following are properties of Sustained Release Systems: Slow Drug Release the drug is released gradually over a prolonged period instead of immediate release [10]. Maintenance of therapeutic level Prolongs the duration of plasma drug level within the therapeutic range for a longer time [11]. Reduced Dosing Frequency Reduces the number of doses needed each day, making it easier for people to take [8]. Improved Patient

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Compliance treatment schedules are easier to follow due to the reduced number of treatments administered.

Patients can adhere to treatment schedules easier due to less treatment administration [9]. Reduced side effects avoid rapid surge in the level of the drug and reduces toxicity effect [12]. Uniform Drug Absorption Gives constant absorption and action of medication [10]. Enhanced Therapeutic Effect Sustains the effect of the drug [11]. Use of Polymers or Matrix Systems Sustained release formulations are generally prepared by controlling the release of the drug from the formulation with polymers, coatings or matrix [12].

Advantages of controlled and sustained drug delivery system

Improve patient adherence and ease. Decreased dose requirement. Less variation in blood drug concentration. More uniform effect. Employ less total drug that will: Minimises or prevents local side effects Reduce and/or prevent systemic adverse reactions Reduce and/or prevent systemic adverse reactions**.** Does not become as tolerant or sensitized to the effects of drugs over time. Safety margin of potent drug is increased by technically excellent designing of the formulation [13].

Disadvantages of controlled and sustained drug delivery system

More costly processes and equipment are needed in the manufacturing of these dosage forms. The dosage regimen is fixed; the physician has less flexibility in changing the dosage regimen as this is fixed by the Design of the dosage form. Risk of dose dumping, usually it contains drug amount that Conventional formulations are approximately 1/3 the strength of or less than its counterparts. This may be a lot of drugs get quickly released leading to toxicity Medication may not work as quickly as usual if it is absorbed less than usual. The impact of feed on pharmaceuticals absorption the kinetics can be very different between various formulations of a Systemic release. The drugs which are absorbed at a particular time in Gastro intestinal tract cannot be formulated in this type of system. Increased potential for the first pass clearance. For oral effective drug release is influenced and limited by Gastro Intestinal residence time. These are designed for a normal population that is on the basis of the biological half-lives. Since disease state which changes drug dispositions, together with interpatient variability in drug disposal, can both be a factor, these should be considered. These pharmacokinetic parameters are not included. Enzymes in the intestine can act on drugs to a great extent: As the drug stays in the body for a longer period of time, breakdown will occur. In case of accidental failure of the product effective antidote may be difficult to employ [14].

Objective of this review

The purpose of controlled and sustained release systems is to provide to achieve a constant plasma concentration of the drug for an extended period of time [15]. To decrease the number of doses and increase patient adherence [16]. To avoid peak–trough drug level fluctuations that lead to fewer side effects and less toxicity [15, 17]. To improve bioavailability of drugs with short biological half-life [16]. To ensure the best control of therapy and its overall therapeutic effectiveness [17]. To lower the cost of health care because of enhanced treatment outcomes and cost effectiveness [15]. To avoid destruction of drug molecules in the gastrointestinal tract to provide localized or targeted delivery of drugs where necessary [17].

Table 1.1 Difference between controlled and sustained drug delivery system

S. No	Dimension	Controlled release	Sustained release	Reference
1.	**Primary mechanism**	Diffusion/ matrix erosion	Osmosis/reservoir surface erosion	[18]
2.	**Release kinetics**	First-order or Higuchi	Zero – order(ideally)	[19]

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3.	**Rate predictability**	Variable, environment Dependent	Predetermined, environment Independent	[20, 21]
4.	**Design complexity**	Moderate	High (engineered membranes)	[23, 24]
5.	**Therapeutic precision**	Moderate	High	[25,26]

FUNDAMENTALS OF CONTROLLED AND SUSTAINED RELEASE SYSTEM

Controlled and sustained release drug delivery systems are advanced pharmaceutical technologies developed to ensure the constant release of the drug in the body for an extended period of time by controlling the rate, time and location of drug release. They eliminate the problems associated with conventional dosage forms of frequent dosing, changing levels of plasma drug, and patient noncompliance. The systems are designed in the light of integration of pharmaceutics, pharmacokinetics, and polymer science [18]. The ultimate goal is to maximize therapeutic benefit at a safe, effective concentration of the drug and to minimize its potential for toxicity and sub-therapeutic levels [19].

Basic Principles

The basic idea of controlled and sustained release systems is to make the drug release rate as similar as possible to the rate of elimination. Controlled Drug Release Rate This is the first of a new series of articles on the Controlled Drug Release Rate. Drug is released at a set rate and not all at once, providing a more sustained therapeutic activity. Maintenance of Steady-State Concentration The system has been designed to keep the plasma drug level constant by keeping the rate of absorption equal to the rate of elimination [19]. Reduction of peak-through fluctuations Minimization of Peak–Trough Fluctuations Effect of the avoidance of sudden changes in drug level: adverse effects and therapeutic failure are minimized [20]. Use of Rate-Controlling Mechanisms The use of mechanisms to control the reaction rate. The drug release is controlled by a diffusion, dissolution, or osmotic pressure or polymer degradation mechanism [21].

Pharmacokinetic Considerations

Pharmacokinetics is very important in the design of controlled release system as it indicates the behaviours which the drug undergoes in the body. Absorption Drugs need to be taken all over the gastrointestinal tract. Drugs that have a narrow absorption window (such as upper intestine only) are not as well suited [19]. Distribution For drugs which have high volume of distribution, controlled systems may require higher loading doses to establish therapeutic plasma levels [20]. Metabolism First-pass metabolism can decrease bioavailability of drugs with extensive first-pass metabolism, and controlled systems can be helpful in this regard by providing a sustained input [18]. Elimination Half-Life Short half-life drugs (2-8 hours) are best candidates because these systems help to lengthen the effect of the drugs [21]. Therapeutic Window A narrow therapeutic window is more demanding in terms of release rate control to prevent toxicity [19].

Ideal Drug Candidates

Not all drugs are suitable for controlled and sustained release formulations. Ideal candidates should have Moderate Biological Half-Life a drug that has a very short half-life or very long half-life is not optimal [18].

Low to Moderate Dose Large dosage sizes that are hard to formulate can be a problem with high dose drugs [20]. Good Absorption Characteristics Ideally, drugs should be equally absorbed in the

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gastrointestinal tract [19]. Stability in GI Environment Drugs should not be decomposed in the stomach or gut [21]. Wide Therapeutic Index To reduce risk of toxicity due to accidental dose dumping [18]. Non-Irritant Nature Gastrointestinal irritation should not occur on long-term exposure to drugs [20].

Factors affecting drug release

1.1 Polymer and Excipient Factors

Polymer Type Hydrophilic polymers swell and provide gel barriers, and hydrophobic polymers (e.g., ethyl cellulose) control diffusion. Molecular Weight A high molecular weight polymer will have a low rate of drug release [20]. Cross-Linking Density The more cross-linked, the less porosity and the slower the release rate [18]. Swelling and Erosion Behaviour. Diffusion is inhibited by swelling and is accompanied by progressive breakdown of the matrix in the case of erosion [21].

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1.3 System Design Factors

Types of Delivery system Matrix systems, Reservoir systems, Osmotic systems, Drug Loading the amount of drug may increase the release rate because of the greater concentration difference [19]**.** Coating Thickness For a coated system, the thicker coating decreases the drug diffusion rate [20].

1.4 Physiological Factors

Gastrointestinal pH Drug solubility and the behaviour of the polymers are influenced by pH changes [18]. Gastric Emptying Time Rapid gastric emptying can decrease residence time and release [21]. Food Intake Food can slow down emptying of the stomach that may affect the absorption of drugs [19]. Enzymatic Activity Drug or polymer matrix can be broken down by enzymes [20]. Manufacturing Factors Compression Force Gives rise to porosity and hardness of tablets; impacts drug release [18]. Mixing Uniformity Provides uniform distribution of drugs in matrix systems [21]. Granulation Method The presence of wet/dry granulation influences the particle size and release behaviour [19].

CLASSIFICATION OF CONTROLLED AND SUSTAINED DRUG DELIVERY SYSTEM Matrix Systems

One of the most popular sustained and controlled drug delivery systems is the matrix system. A uniform dispersion of the drug in a polymer matrix is characterized and, in such systems, the drug is released primarily by diffusion and/or erosion processes. Matrix systems are easy to produce, inexpensive and have a long therapeutic duration [22].

2.1 Hydrophobic

Hydrophobic matrix systems use polysaccharides or waxes that are not soluble in water to slow the release of the drug. These can be made from ethyl cellulose, polyethylene, hydrogenated vegetable oils, and carnauba wax. The dosage form is placed into gastrointestinal fluids and the aqueous media permeate it via pores and channels, allowing a slow diffusion of the dissolved drug outwards [23]. In the case of hydrophobic matrices, the release of drugs is mostly controlled byThe transport of drugs through tortuous channels. Matrix porosity Polymer concentration the size of the particles of the drug. These systems are particularly useful for water-soluble drugs because the matrix is insoluble which helps to retard the dissolution rate. However, the release of the drug may not be complete because

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the drug could be entrapped inside the matrix core [24]. Advantages**s**The formulation and scale-up of the product is easy. Good physical stability Acceptable for high dose medications Limitation**s** In some cases, the possibility of dose dumping has been mentioned. The matrix which remains behind after the drug has been released Less preferred to poorly soluble drugs.

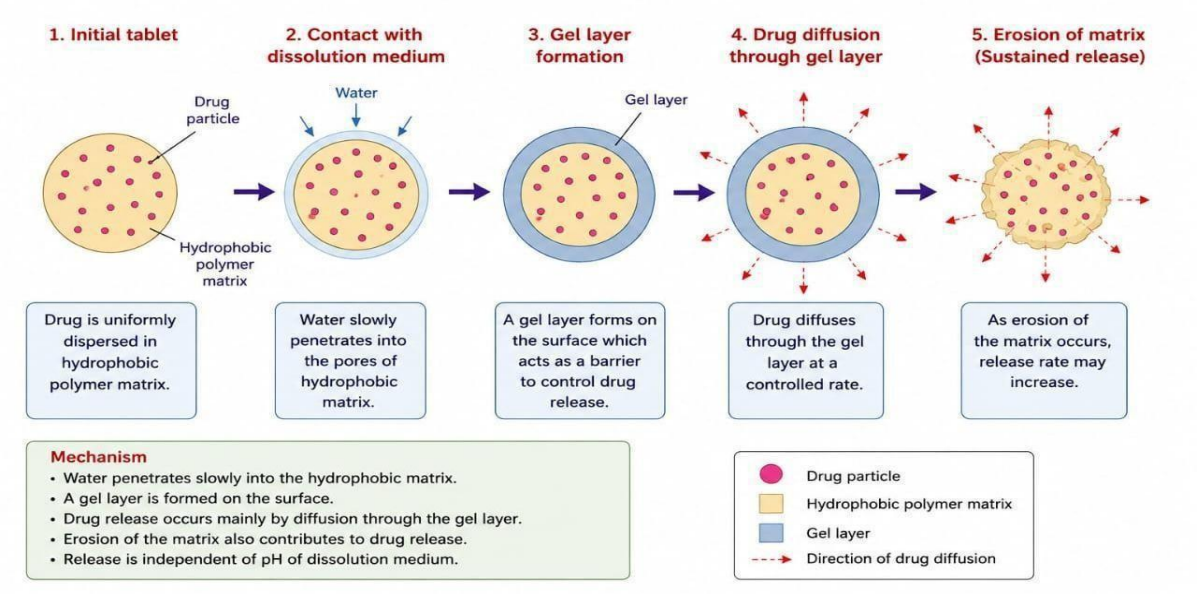

Fig. 1.1 Hydrophobic matrix

2.2 Hydrophilic Matrix Systems

Hydrophilic matrix systems are based on hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, hydroxyethyl cellulose and xanthan gum, which are swellable polymers. When placed in water, the polymer absorbs the water and becomes a gel that coats the tablet surface [25]. Drugs are released by: Water infiltration into matrix. Water infiltration into matrix the swelling of polymers and the formation of gels Gradual polymer erosion Two important factors, viscosity and concentration of the polymer, have a significant effect on release kinetics. Flexibility, biocompatibility and predictable release profiles are the several reasons why hydrophilic matrices are widely used [26]. Advantage**s** Excellent patient compliance Uniform drug release Low manufacturing cost good safety profile Limitations The swelling of polymers and the formation of gels Sensitive to the pH and motility of the gut.

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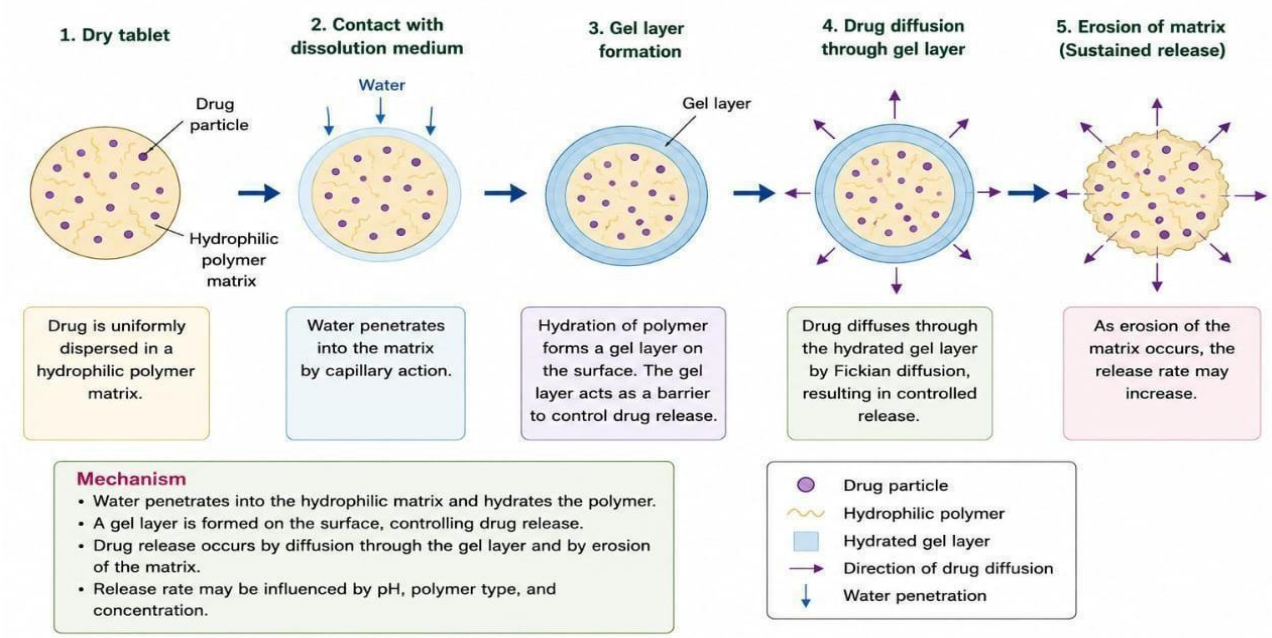

Fig. 1.2 Hydrophilic Matrix

Reservoir controlled systems

Reservoir systems are comprised of a drug core encapsulated by a rate controlling polymer membrane. The membrane controls the diffusion of the drugs from the central reservoir to the body fluids [27]. The membranecan be made out of polymers like Ethyl cellulose Polyvinyl acetate Silicone elastomers Polyurethane The release of a drug is governed by Fick's law of diffusion and is dependent upon Membrane thickness Drug solubility Diffusion coefficient Surface area of the system These systems can provide near zero order release kinetics, thus keeping the plasma drug concentration constant over long periods of time [28]. Examples Transdermal patches Coated pellets Implantable devices Advantages Precise release of the drug Reduced dosing frequency Improved therapeutic efficiency reduced side effects.

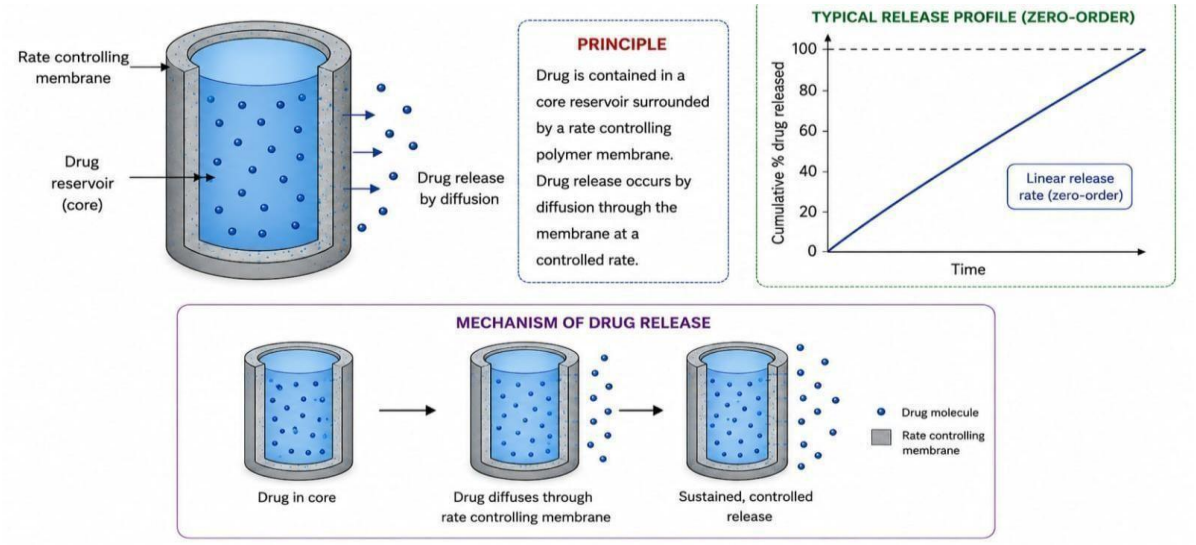

Fig. 1.3 Reservoir controlled system

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Osmotic drug delivery systems (osmotic pumps)

The osmotic drug delivery systems make use of the osmotic pressure for the controlled release of drugs. These systems consist of an osmotic agent and drug(s) in the core which is surrounded by a semi-permeable membrane [29]. The gastrointestinal fluid's osmotic pressure is responsible for transporting water across the semi permeable membrane. The water consumed dissolves the drug and the solution is pumped out through a delivery hole with a controlled rate Types of Osmotic Pump Elementary Osmotic Pump It is a feature added in 2014. Has one drug compartment and one delivery orifice. Push–Pull Osmotic Pump Made for poorly soluble drugs, with separate push and drug layers. Controlled-porosity osmotic pump Plastic Batch Osmotic Pump Includes pore forming agents which form microporous channels upon hydration**.** Advantage**s** Predictable zero-order release the effect of pH and food is reduced. The high in vivo–in vitro correlation is the value that is most important. Limitations Expensive manufacturing A special type of equipment is required. A risk of membrane failure is present. There is a risk of membrane failure. Examples Osmotic controlled release oral delivery system tablets and Nifedipine osmotic systems.

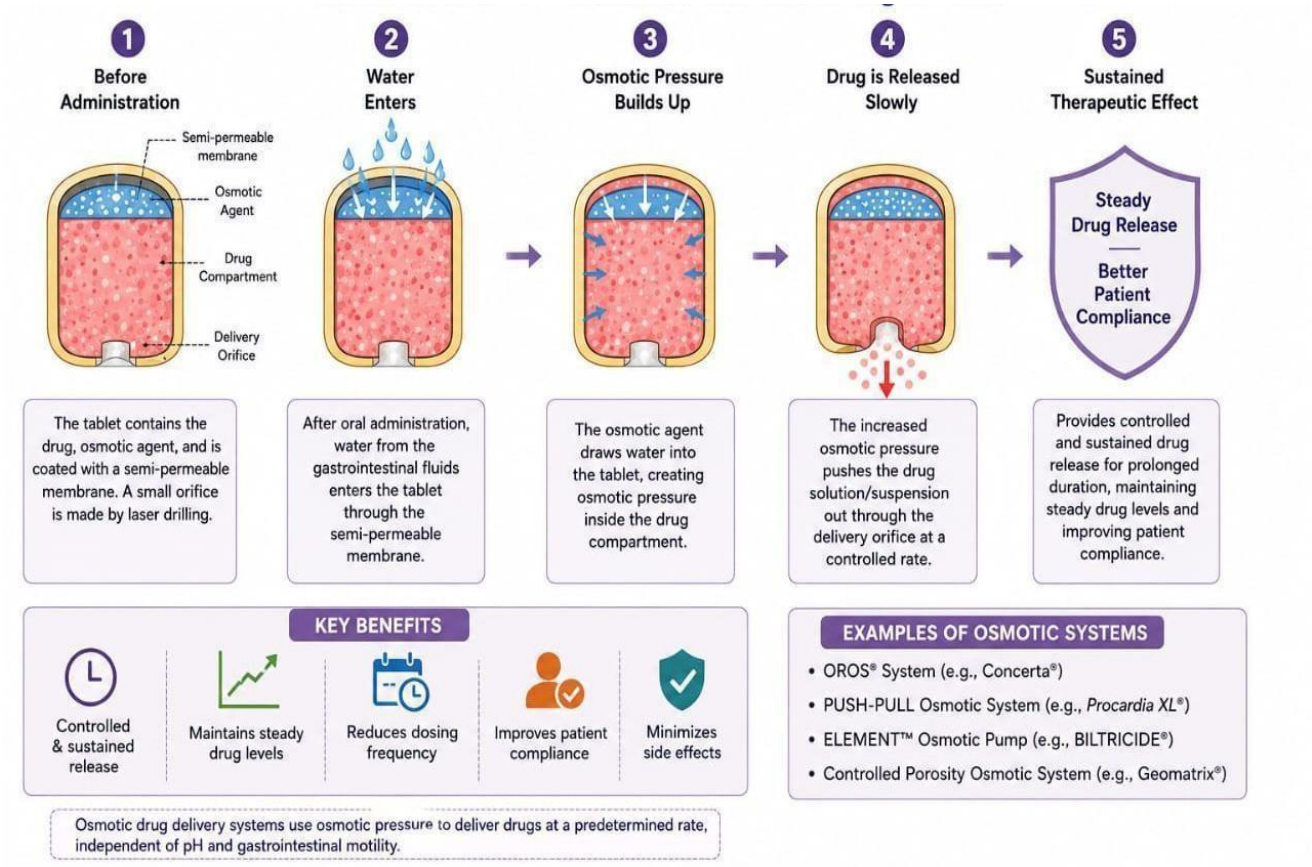

Fig. 1.4 Osmotic Drug Delivery Systems

Multiarticulate system

Multiarticulate drug delivery systems are composed of several small discrete units that are able to deliver the drug in a controlled manner. These systems enhance drug delivery across the gastrointestinal tract and reduce irritation in the area [31]. Pellets are spherical aggregates 0.5–1.5 mm in diameter made by the process of spherization, extrusion-spherization, or by spray drying. Rate controlling polymers are used for coating pellets to affect the release of drugs [32].

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Advantages Uniform gastric emptying Reduced dose dumping flexible formulation Beads are small spherical particles produced mainly using ionotropic gelation techniques. Typically, natural polymers, like alginate and chitosan, are used [33]. Beads are particularly useful for Site-specific delivery Colon targeting Protein and peptide delivery Microspheres The microspheres are free flowing spherical particles that have drug dispersed within the polymer matrix. Usually, the size is 1-1000µm [34]. Common polymers include: PLGA Polylactic acid Albumin The mechanisms for drug release are: Diffusion Polymer erosion Swelling Advantages Slow release over extended periods of time Targeted delivery capability Reduced toxicity Limitations Complex manufacturing.

Novel drug delivery systems

New drug delivery systems aim to increase therapeutic effectiveness, site specificity, bioavailability, reduce toxicity and side effects [35]. Lipid-Based System the lipid-based systems are liposomes, solid lipid nanoparticles nanostructured lipid carriers and self-emulsifying drug delivery systems [36]. These systems improve Poorly water-soluble drugs are the ones that have low solubility. Lymphatic absorption drug stability Liposomes are vesicles composed of phospholipids which can encapsulate both hydrophilic and lipophilic drugs. Advantages Biocompatibility Reduced Toxicity Enhanced bioavailability.

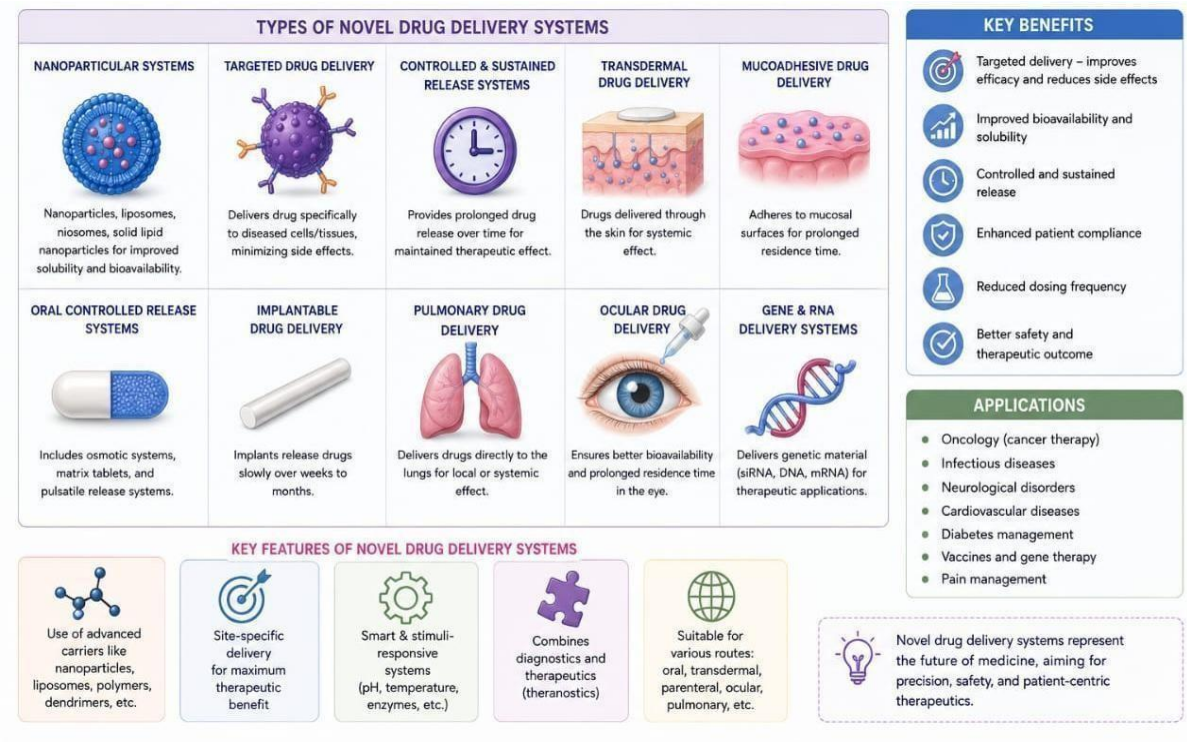

Fig. 1.5 Novel Drug Delivery System

3.1 Polymeric Systems

Polymeric drug delivery systems use polymers (natural or synthetic) for controlled release applications [37]. Common polymers: Chitosan Alginate these systems may be: Biodegradable Mucoadhesive Stimuli-responsive Applications include Cancer therapy Vaccine deliveryImplantable systems.

3.2 Nano-Based Systems

Nano-based drug delivery systems use nanoparticles that are generally 1 – 100 nm. These systems improve cellular

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uptake, targeted delivery and therapeutic effects [38]. Types include: Polymeric nanoparticlesMetallic nanoparticlesNanocrystals Nanocarriers can be used to pass the biological barriers and achieve active or passive targeting to diseased tissues [39]. Advantages Enhanced bioavailability Controlled and targeted releaseReduced systemic toxicity Limitations Potential nanotoxicity Scale-up challenges Regulatory concerns.

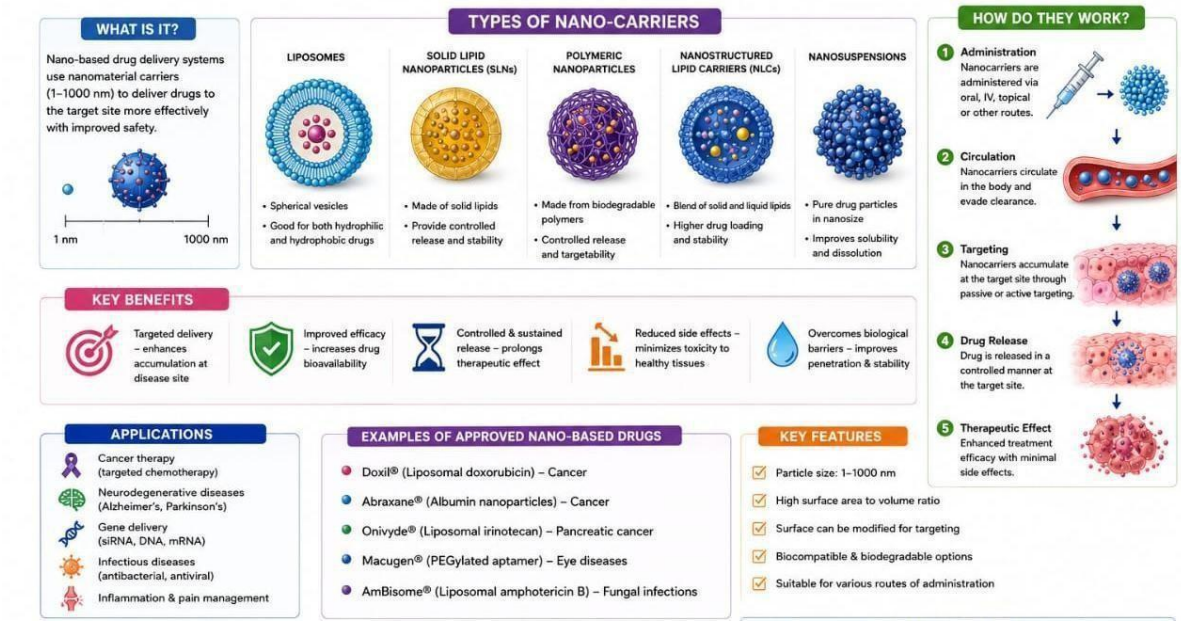

Fig. 1.6 Nano Based Drug Delivery System

MECHANISMS OF DRUG RELEASE

Diffusion-Controlled Release

Diffusion-controlled release is one of the most fundamental and widely studied mechanisms governing drug liberation from controlled delivery systems [40]. In this mechanism, the drug molecules migrate from a region of higher concentration within the dosage form to a region of lower concentration in the surrounding biological environment, driven by a concentration gradient across the system [41]. Fick's first law states that the rate of drug transfer per unit area is proportional to the concentration gradient, and this relationship forms the theoretical basis for designing reservoir and matrix-type diffusion systems [43]. In reservoir-type devices, the drug core is surrounded by a rate-controlling polymeric membrane, and the drug must diffuse through this membrane to reach the dissolution medium [44]. The membrane thickness, permeability, and surface area are carefully engineered to achieve a desired release rate [45]. In contrast, matrix-type systems disperse the drug uniformly throughout a polymeric matrix, and the drug diffuses through the tortuous pathways of the polymer network to reach the external environment [46]. The Higuchi model is one of the earliest and most widely applied mathematical models for describing diffusion-controlled drug release from matrix systems, where cumulative drug release is proportional to the square root of time [47].

The model assumes a homogeneous matrix, perfect sink conditions, and that the initial drug loading is significantly higher than the drug's solubility in the matrix [49]. For reservoir systems, zero-order release kinetics can be achieved when the drug concentration inside the reservoir remains constant, providing a steady driving force for diffusion across the membrane [50]. This zero-order release is often considered the "gold

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standard" of controlled drug delivery because it maintains a constant drug concentration within the therapeutic window over prolonged periods [51]. The diffusion coefficient of the drug through the polymer is a critical parameter that depends on the physicochemical properties of both the drug and the polymer, including molecular weight, crystallinity, cross-linking density, and the degree of swelling in biological fluids [52]. Hydrophilic polymers tend to swell upon contact with aqueous media, which increases the pore size and free volume within the matrix, thereby facilitating drug diffusion [53]. Conversely, hydrophobic polymers resist water penetration and maintain tighter molecular networks, leading to slower and more sustained diffusion-controlled release profiles [54]. Temperature also influences diffusion rates, as increased molecular kinetic energy at higher temperatures enhances the mobility of drug molecules through the polymeric matrix [55]. The Korsmeyer Peppas model, also known as the power law model, is frequently employed to distinguish between Fiskian and non-Fiskian transport mechanisms by analyzing the release exponent [56].

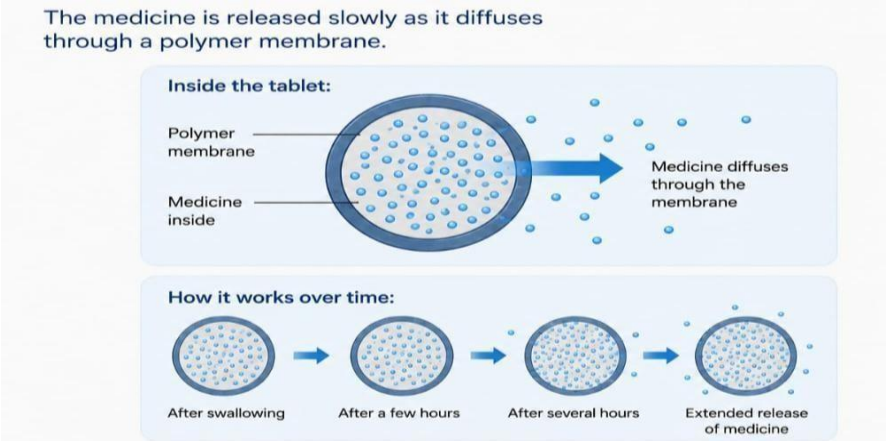

Fig. 1.7 Diffusion controlled release

Dissolution-Controlled Release

Dissolution-controlled release systems operate on the principle that the drug is released as the carrier material or the drug itself dissolves in the surrounding biological fluids [40]. In these systems, the rate-limiting step is the dissolution of the drug particles or the dissolution of a coating material that encapsulates the drug [41]. The Noyes-Whitney equation provides the fundamental mathematical framework for understanding dissolution-controlled release, relating the dissolution rate to factors such as the surface area of the dissolving solid, the diffusion coefficient, the saturation solubility, and the thickness of the stagnant diffusion layer [42]. According to this equation, dissolution rate can be enhanced by increasing the surface area of drug particles through micronization or nanonization, by improving the solubility through salt formation or amorphous solid dispersions, or by reducing the diffusion layer thickness through agitation [43]. Dissolution-controlled systems can be broadly categorized into two types: encapsulation dissolution systems and matrix dissolution systems [44]. In encapsulation dissolution systems, the drug particles or tablets are coated with a slowly dissolving polymer or wax layer, and the drug is released only after the coating has dissolved [45]. The thickness and composition of the coating determine the lag time before drug release commences and the overall rate of dissolution [46]. Matrix dissolution systems, on the other hand, incorporate the drug within a slowly dissolving or erodible matrix, and drug release occurs

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as the matrix material gradually dissolves in the surrounding medium [47].

The dissolution rate is influenced by the pH and ionic strength of the gastrointestinal fluids, which can significantly affect the solubility of both the drug and the carrier [48]. For weakly acidic drugs, dissolution is faster in alkaline environments, while weakly basic drugs dissolve more readily in acidic conditions, a relationship described by the Henderson-Hasselbalch equation [49]. Temperature plays a critical role in dissolution-controlled release, as the solubility of most solid drugs increases with rising temperature, thereby accelerating the dissolution process [50]. The particle size and morphology of the drug also profoundly influence dissolution kinetics; smaller particles with greater surface-area-to-volume ratios dissolve more rapidly [51]. Polymorphic forms and amorphous states of a drug can exhibit significantly different dissolution rates due to differences in lattice energy and molecular packing [52]. Amorphous forms, which lack long-range molecular order, generally have higher free energy and therefore dissolve faster than their crystalline counterparts [53].

However, amorphous drugs may recrystallize during storage, necessitating the use of polymeric stabilizers to maintain the amorphous state [54]. The design of dissolution-controlled formulations requires careful selection of excipients and coating materials that match the desired dissolution profile, whether it is immediate release, extended release, or delayed release targeting a specific region of the gastrointestinal tract [56].Dissolution testing using standardized apparatus (USP Apparatus I and II) is a critical quality control tool used to evaluate and compare the in vitro performance of dissolution-controlled formulations [57]. The development of biorelevant dissolution media that mimic gastric and intestinal fluid conditions has further improved the in vitro–in vivo correlation for these systems [58]. Overall, dissolution-controlled release remains a cornerstone of oral drug delivery, offering a straightforward and cost-effective approach to modulating drug release profiles [59].

Erosion-Controlled Release

Erosion-controlled release systems rely on the gradual degradation or erosion of the polymeric carrier material to regulate the rate and extent of drug release [40, 60]. Erosion can be classified into two distinct types: surface erosion and bulk erosion, each of which produces fundamentally different release kinetics [41, 61]. Surface erosion occurs when the polymer degrades primarily at the outer surface of the dosage form, and the device shrinks over time while maintaining its structural integrity [42, 62]. This mechanism is analogous to the dissolution of a bar of soap, where the material is consumed layer by layer from the outside inward [43]. Surface-eroding polymers, such as polyanhydrides and polyortho esters, are particularly advantageous because they can achieve near-zero-order release kinetics, providing a constant rate of drug release over the lifespan of the device [54, 63]. In surface erosion, the rate of polymer degradation at the surface is much faster than the rate of water penetration into the bulk of the material, ensuring that the erosion front remains confined to the surface [45]. This behavior is typically observed in hydrophobic polymers with water-labile bonds, where the polymer backbone is cleaved by hydrolysis but the hydrophobic nature prevents water from penetrating deep into the matrix [46].

Bulk erosion, in contrast, occurs when water penetrates the entire polymer matrix, and degradation takes place throughout the bulk of the material simultaneously [47, 64]. This is characteristic of polymers such as poly (lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL), where the rate of water ingress exceeds the rate of polymer degradation at the surface [48, 65]. The triphasic release pattern commonly observed with PLGAbased systems is a direct consequence of bulk erosion: the initial burst is due to drug

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near the surface, the lag phase corresponds to slow polymer degradation, and the final rapid phase occurs when the matrix disintegrates [50]. The ratio of lactic acid to glycolic acid in PLGA copolymers is a critical parameter that determines the rate of erosion, as glycolic acid-rich copolymers degrade faster due to their greater hydrophilicity [51]. Higher molecular weight polymers have longer chained that require more hydrolytic cleavage events before the oligomeric fragments become water-soluble and can be released [53].

The presence of acidic end groups can autocatalyze the degradation process, as the local accumulation of acidic degradation products lowers the pH within the matrix and accelerates hydrolysis [54]. Natural polymers such as gelatin, collagen, and chitosan are susceptible to enzymatic degradation by proteases and lysozymes, and this property has been exploited to design enzyme-responsive drug delivery systems [56]. Erosion-controlled systems are widely employed in biodegradable implants, microspheres, and nanoparticles for applications ranging from cancer chemotherapy to vaccine delivery and tissue engineering [57]. The advantage of erosioncontrolled systems is that they eliminate the need for surgical removal of the device after drug depletion, as the polymer is completely resorbed by the body [58]. The degradation products of these polymers, such as lactic acid and glycolic acid from PLGA, are natural metabolites that are safely eliminated through normal metabolic pathways [59]. Careful selection of polymer composition, molecular weight, and device geometry allows precise tailoring of the erosion rate to match the therapeutic requirements [60].

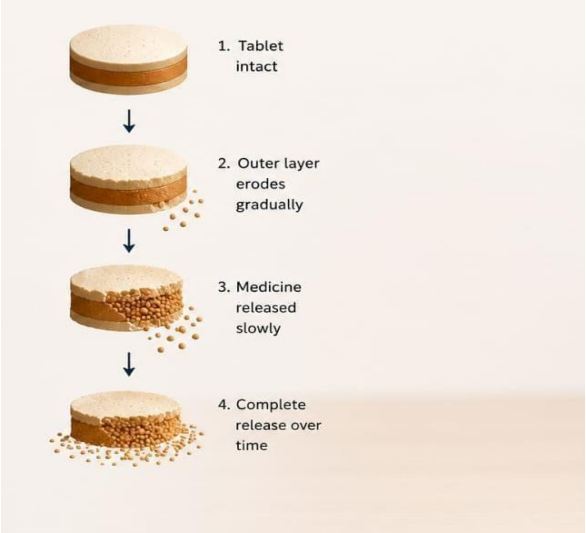

Fig. 1.8 Erosion controlled Release

Osmotic Pressure-Controlled Release

Osmotic pressure-controlled release systems utilize the principle of osmosis to drive drug release at a controlled and predictable rate [40, 66]. These systems consist of a drug core surrounded by a semipermeable membrane that allows the influx of water but restricts the outflow of drug and osmotic agents [41]. The semipermeable membrane is typically made from cellulose acetate, and a small orifice is drilled through the membrane using a laser to create a delivery port [42]. When the system is exposed to an aqueous environment, water is drawn into the core through the semipermeable membrane due to the osmotic pressure difference between the inside and outside of the system [43]. The influx of water dissolves the drug and the osmotic excipients, creating a concentrated drug solution or suspension inside the core [44]. The elementary osmotic pump, first conceptualized by Theeuwes in 1975, is

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the simplest osmotic delivery device and consists of a single compartment system containing the drug mixed with an osmogent [46]. For drugs with low aqueous solubility, the push-pull osmotic pump was developed, which features a bilayer tablet with a drug layer and a push layer that expands upon hydration to displace the drug formulation through the delivery orifice [47].

The rate of drug delivery from osmotic systems is determined by the osmotic pressure gradient, the permeability and thickness of the semipermeable membrane, and the size of the delivery orifice [48]. Unlike diffusion-controlled systems, osmotic delivery systems can achieve true zero-order release kinetics that are largely independent of the drug's physicochemical properties and the pH and hydrodynamic conditions of the gastrointestinal tract [49]. This pH-independent release behavior is a major advantage over conventional matrix systems, which are often affected by the varying pH conditions along the gastrointestinal tract [50]. The osmotic pressure is generated by water-soluble osmogents such as sodium chloride, potassium chloride, mannitol, or fructose incorporated into the drug core [51]. The osmotic pressure difference across the membrane can be substantial, often reaching several hundred atmospheres, providing a strong and consistent driving force for drug release [52]. The semipermeable membrane must possess appropriate mechanical strength to withstand the internal pressure without rupturing, while maintaining sufficient permeability to allow adequate water influx [53]. Cellulose acetate is the most commonly used membrane material due to its excellent semipermeable properties, biocompatibility, and ease of processing by coating techniques [54].

The addition of plasticizers such as polyethylene glycol (PEG) or triethyl citrate to the membrane formulation can modify the membrane flexibility and water permeability [55]. Pore-forming agents such as sorbitol can also be incorporated into the membrane to create micropores upon dissolution, further modulating the water influx rate [56]. Osmotic systems have been successfully commercialized for a wide range of therapeutic agents, including cardiovascular drugs (nifedipine in Procardia XL), central nervous system drugs (methylphenidate in Concerta), and antidiabetic medications (glipizide in Glucotrol XL) [57]. The controlled porosity osmotic pump is a modification where the membrane contains water-soluble additives that leach out upon contact with aqueous media, creating in situ micropores that eliminate the need for laser drilling [58]. Despite their advantages, osmotic systems involve complex manufacturing processes and higher production costs compared to conventional matrix tablets [59]. The performance of osmotic systems can be affected by the mechanical integrity of the membrane during transit through the gastrointestinal tract, and any damage to the membrane can lead to dose dumping [60]. Nevertheless, osmotic pressure-controlled systems represent one of the most sophisticated and reliable approaches to achieving constant-rate drug delivery [61].

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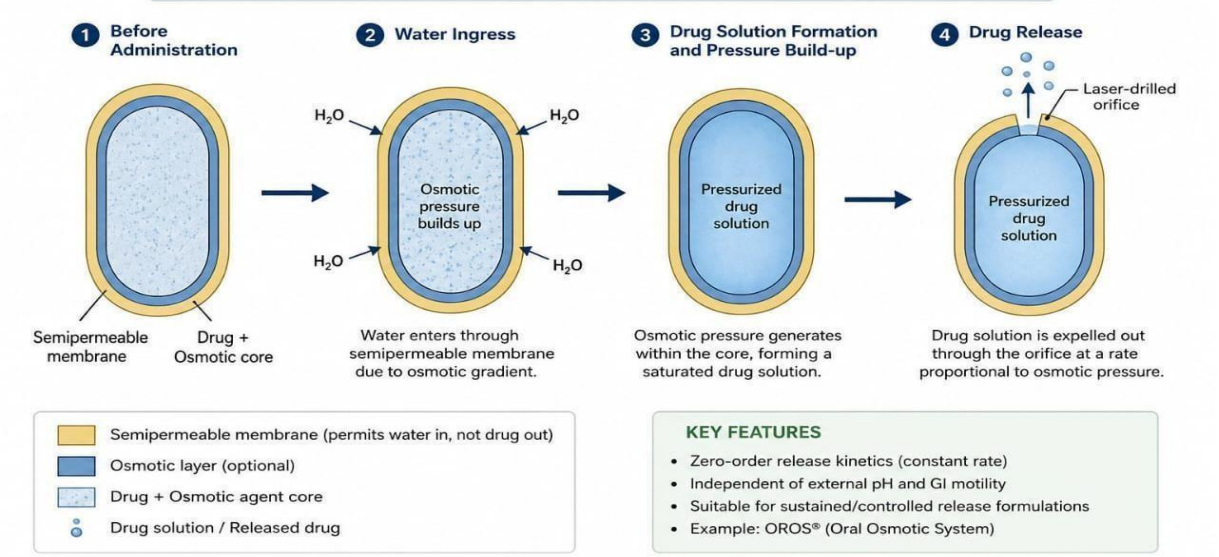

Fig. 1.9 Osmotic pressure-controlled release

Stimuli-Responsive Release (pH, Temperature, Enzymes)

Stimuli-responsive drug release systems, also known as "smart" or "intelligent" delivery systems, represent a paradigm shift in controlled drug delivery by enabling on-demand drug release in response to specific environmental triggers [40, 67]. Unlike conventional controlled release systems that release drugs at predetermined rates regardless of physiological conditions, stimuli-responsive systems sense changes in their microenvironment and alter their physicochemical properties accordingly to modulate drug release [41, 68]. These systems can respond to a wide variety of internal biological stimuli, including pH, temperature, enzymes, redox potential, and glucose concentration, as well as external physical stimuli such as light, magnetic fields, ultrasound, and electric fields [42, 69]. The concept of stimuli-responsive delivery is rooted in the design of "smart" polymeric materials that undergo reversible or irreversible structural transitions in response to specific cues [43].

pH-Responsive Release: pH-responsive systems are among the most extensively investigated stimuli responsive platforms, owing to the significant pH variations that exist across different physiological compartments and disease states [44]. The gastrointestinal tract exhibits a dramatic pH gradient, ranging from pH 1.0–3.0 in the stomach to pH 6.5–7.5 in the intestines, and this natural gradient can be exploited for sites specific oral drug delivery [45]. Tumor microenvironments are known to be more acidic (pH 6.5–6.8) than normal tissues (pH 7.4) due to the Warburg effect and enhanced glycolysis, and pH-sensitive nanocarriers can be designed to preferentially release their drug payload in this acidic milieu [46]. pH-responsive polymers contain ionizable functional groups, such as carboxylic acids or amino groups, that undergo protonation or deprotonation at specific pH values [47]. Anionic polymers, such as poly (acrylic acid) and Eudragit L and S series, contain carboxylic groups that are protonated and uncharged at low pH (remaining collapsed) but become ionized and swell at higher pH, releasing the entrapped drug [48]. Cationic polymers, such as chitosan and polyethylenimine, behave in the opposite manner, becoming protonated and swollen at acidic pH and deswelling at neutral or alkaline pH [49]. Enteric coatings based on pH-responsive polymers are a well-established pharmaceutical technology used to protect acid-labile drugs from the harsh gastric environment and deliver them to

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the intestinal region where they are absorbed [50].

Temperature-Responsive Release: Temperature-responsive drug delivery systems are designed around polymers that exhibit a lower critical solution temperature or an upper critical solution temperature in aqueous solution [52]. Poly(N-isopropylacrylamide) is the most widely studied Thermoresponsive polymer, with an lower critical solution temperature of approximately 32°C in pure water, which is close to physiological skin temperature [53]. Below the low critical solution temperature, poly(N-isopropylacrylamide) chains are hydrated and extended in solution, forming a swollen hydrogel network [54]. This temperature-induced phase transition has been exploited to design injectable hydrogels that are liquid at room temperature for easy administration but gel rapidly at body temperature to form a drug depot in situ [56]. By copolymerizing poly (Isopropylacrylamide) with hydrophilic or hydrophobic monomers, the low critical solution temperature can be fine-tuned to match the desired transition temperature for specific clinical applications [57]. Localized hyperthermia, often achieved through external heating or by incorporating magnetic nanoparticles that generate heat under an alternating magnetic field, can be used to trigger on-demand drug release from thermoresponsive carriers at the target site [58]. Thermoresponsive liposomes containing thermosensitive lipids release their drug payload when heated above a critical temperature, combining the targeting advantages of liposomes with the temporal control of thermoresponsive systems [59].

Enzyme-Responsive Release: Enzyme-responsive drug delivery systems exploit the overexpression of specific enzymes in pathological tissues to achieve site-selective drug release [60]. Enzymes such as matrix metalloproteinases, cathepsins, hyaluronidases, and phospholipases are upregulated in tumor microenvironments, sites of inflammation, and infected tissues [61]. Polymer–drug conjugates, in which the drug is covalently attached to a polymer backbone through an enzyme-cleavable linker, represent a classic example of enzyme-responsive drug delivery [63]. Peptide-based linkers, such as the Gly-Phe-Leu-Gly sequence that is cleaved by lysosomal cathepsin B, have been extensively used in polymer–drug conjugates for anticancer therapy [64]. Hydrogels cross-linked with enzyme-degradable peptide sequences can undergo controlled disassembly in the presence of specific proteases, providing a mechanism for enzyme-triggered drug release within the extracellular matrix [65]. Lipid-based nanoparticles can be engineered with enzyme-responsive components, such as phospholipids that are hydrolyzed by phospholipase A_2, which is overexpressed at inflammatory and tumor sites [66]. Multi-stimuli-responsive systems that combine two or more triggers (e.g., pH and temperature, or pH and enzymes) offer even greater precision in spatial and temporal control of drug release [67]. These dual-responsive systems can be designed to require simultaneous or sequential stimuli for activation, reducing the likelihood of premature drug release and improving therapeutic specificity [68].

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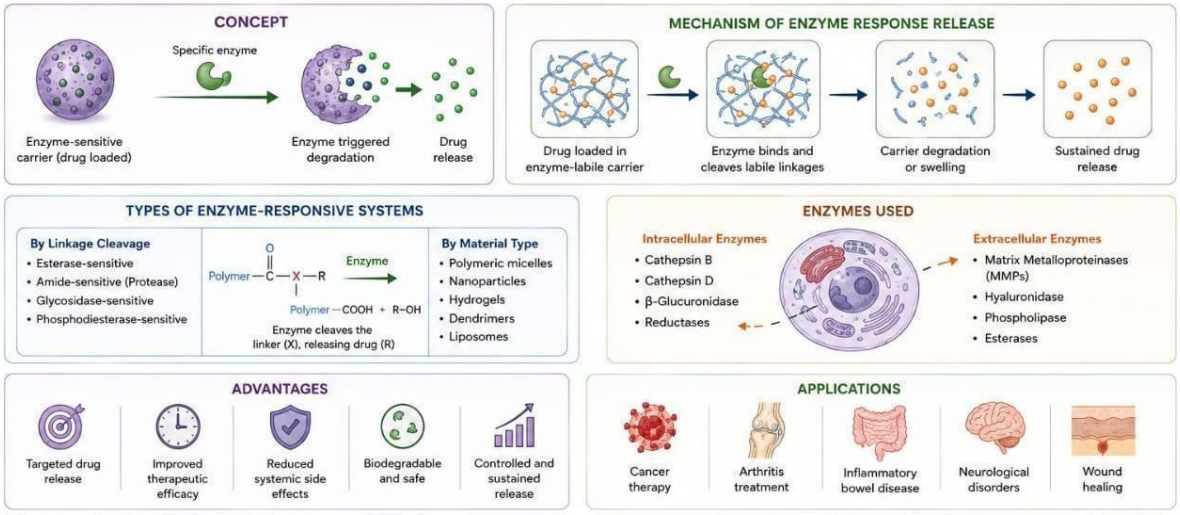

Fig. 2.0 Enzyme responsive release

MATERIALS USED

Polymers (Natural and Synthetic)

Polymers used in drug delivery can be broadly categorized into natural polymers derived from biological sources and synthetic polymers manufactured through chemical polymerization processes [43].

5.1 Natural Polymers:

Natural polymers are obtained from plant, animal, and microbial sources and are generally characterized by excellent biocompatibility, biodegradability, and low toxicity [44]. Chitosan, a cationic polysaccharide derived from the deacetylation of chitin found in crustacean shells, is one of the most widely used natural polymers in drug delivery [45]. Its mucoadhesive properties enable prolonged contact with mucosal surfaces, enhancing drug absorption across epithelial barriers in oral, nasal, and ocular delivery [46]. Chitosan is also pH-responsive, being soluble in acidic conditions due to protonation of its amino groups, which makes it suitable for designing pH-triggered release systems targeting the gastric environment [47]. Alginate, an anionic polysaccharide extracted from brown seaweed, forms hydrogels through ionic cross-linking with divalent cations such as calcium, and is widely used for encapsulation of drugs, proteins, and cells [48]. Gelatine, derived from the hydrolysis of collagen, is a versatile biopolymer used in capsule shells, microspheres, and nanoparticles due to its excellent film-forming properties and enzymatic biodegradability [51]. Hyaluronic acid, a glycosaminoglycan found in the extracellular matrix, has gained significant attention as a drug delivery material due to its ability to target CD44 receptors overexpressed on many cancer cells [52]. Guar gum and xanthan gum are galactomannans and polysaccharides, respectively, used as hydrophilic matrix formers that swell and form viscous gel layers to retard drug release [54].

5.2 Synthetic Polymers:

Synthetic polymers offer the advantage of precisely controlled molecular weight, composition, architecture, and degradation rate, enabling the design of delivery systems with tailored release profiles [55][42]. Poly (lactic-coglycolic acid) (PLGA) is arguably the most extensively studied and commercially successful biodegradable synthetic polymer in drug delivery [56][43]. PLGA is approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for numerous pharmaceutical and medical device applications [57]. The degradation rate of PLGA can be precisely tuned by

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varying the ratio of lactic acid to glycolic acid monomers, the molecular weight, and the end-group chemistry [58]. Poly (lactic acid) (PLA) is a crystalline, slow-degrading polymer derived from renewable resources that is used in long-term implants and sustained release microspheres [59]. Poly (ethylene glycol) is a hydrophilic, non-biodegradable polymer that is widely used as a surface coating (PEGylation) to confer "stealth" properties to nanoparticles, reducing opsonization and clearance by the reticuloendothelial system and extending systemic circulation time [60][44]. Poly(ε-caprolactone) (PCL) is a semi-crystalline polyester with a slow degradation rate, making it suitable for long-term drug delivery implants and scaffolds lasting several months to years [61]. Eudragit polymers, a family of poly(meth)acrylic acid copolymers, are widely used as enteric coatings and sustained release matrices due to their pH-dependent solubility characteristics [62]. Poloxamers (Pluronics) are triblock copolymers of poly (ethylene oxide) and poly (propylene oxide) that exhibit temperature-dependent self-assembly into micellar structures, making them useful as thermoresponsive drug delivery carriers [64]. The concept of polymer blends and copolymers has expanded the material design space, allowing researchers to combine the desirable properties of multiple polymers to achieve complex release profiles, such as pulsatile or multi-phase release [65].

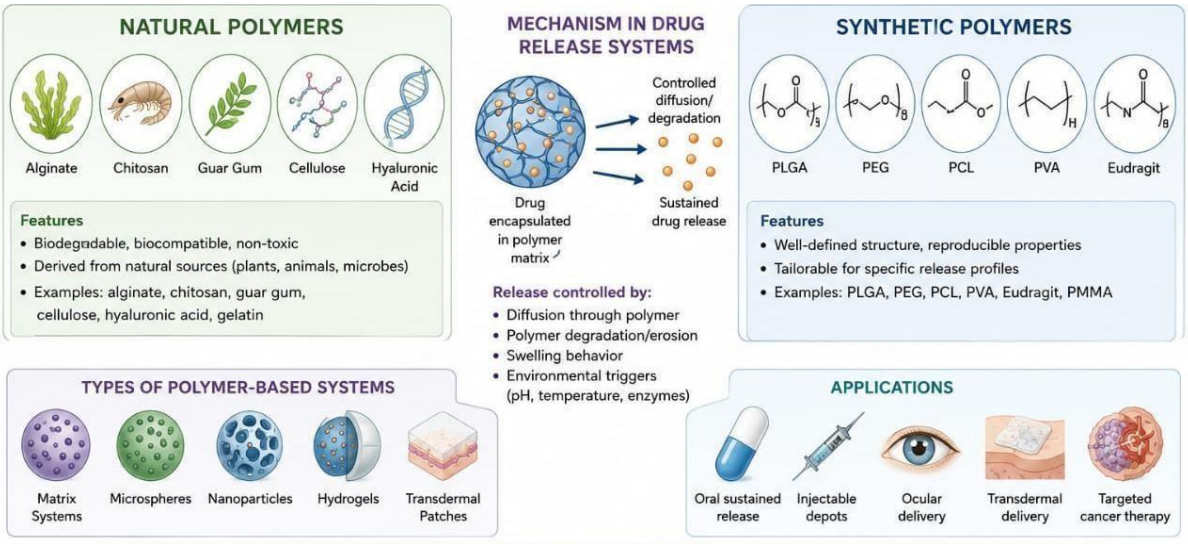

Fig. 2.1 Natural and synthetic polymers

Lipids

Lipids are a diverse class of naturally occurring and semi-synthetic molecules that have become indispensable in drug delivery due to their biocompatibility, ability to encapsulate both hydrophilic and lipophilic drugs, and their capacity to enhance oral bioavailability [40, 45]. Liposomes, which are spherical vesicles composed of one or more phospholipid bilayers surrounding an aqueous core, are the most well-established lipid-based drug delivery systems [41]. The phospholipid bilayer mimics the structure of biological cell membranes, conferring excellent biocompatibility and the ability to encapsulate hydrophilic drugs within the aqueous interior and lipophilic drugs within the lipid bilayer [42]. The development of PEGylated (stealth) liposomes represented a major breakthrough, as the PEG coating dramatically reduced clearance by the mononuclear phagocyte system and extended the circulatory half-life [43]. Doxil was the first FDA-approved nanomedicine, demonstrating the clinical viability of lipid-based nanodrug delivery [44]. Solid lipid nanoparticles are composed of a solid lipid core stabilized by surfactants and represent an alternative to liposomes, polymeric nanoparticles,

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and emulsions for controlled drug delivery [45]. SLNs offer advantages including the use of physiologically well-tolerated lipids, avoidance of organic solvents during preparation, feasibility of large-scale production, and the ability to incorporate both lipophilic and hydrophilic drugs [46].

Nanostructured lipid carriers were developed as a second generation of lipid nanoparticles, incorporating a blend of solid and liquid lipids to create an imperfect crystal structure that accommodates higher drug loading and reduces drug expulsion during storage [47]. Self-emulsifying drug delivery systems and self-nanoemulsifying drug delivery systems (SNEDDS) are isotropic mixtures of oils, surfactants, and co-solvents that spontaneously form fine oil-in-water emulsions or nanoemulsions upon dilution in gastrointestinal fluids, dramatically enhancing the oral bioavailability of poorly water-soluble drugs [48].Lipid–polymer hybrid nanoparticles combine the structural advantages of polymeric cores with the biomimetic properties of lipid shells, offering improved drug loading, controlled release, and enhanced cellular uptake [49]. Lipid nanoparticles (LNPs) have gained tremendous prominence as the delivery vehicles for mRNA vaccines, most notably in the Pfizer BioNTech and Moderna COVID-19 vaccines, demonstrating the transformative potential of lipid-based delivery platforms in next-generation therapeutics [50, 46]. Waxes such as carnauba wax, beeswax, and glyceryl monostearate are used in sustained release matrix tablets and coating formulations to retard drug release through their hydrophobic barrier properties [51]. Phospholipid complexes improve the oral bioavailability of polyphenolic compounds and herbal extracts by forming molecular complexes between phosphatidylcholine and the active ingredient [52]. The versatility of lipids as drug delivery materials stems from their structural diversity, ease of functionalization, scalability of manufacturing, and established safety profile [54].

Biodegradable Materials

The use of biodegradable materials in drug delivery eliminates the need for surgical retrieval of the device after drug exhaustion, a significant clinical advantage over non-degradable implant systems [41]. Poly (lactic-coglycolic acid) is the most prominent biodegradable material used in drug delivery, degrading by hydrolysis of its ester bonds to produce lactic acid and glycolic acid, both of which are natural metabolites of the body [42, 48]. The degradation rate of PLGA is influenced by the copolymer ratio, molecular weight, crystallinity, and the geometry of the device, allowing the release duration to be tailored from weeks to months [43]. Polylactic acid (PLA) exhibits slower degradation compared to Polyhydroxyalkanoates due to the hydrophobic methyl group on the lactic acid monomer, which hinders water penetration and hydrolysis [44]. Polycaprolactone, degrades even more slowly, with degradation times extending from one to several years, making it ideal for long-term implantable drug delivery systems and tissue engineering scaffolds [45]. Polyhydroxyalkanoates are a family of biodegradable polyesters produced by microbial fermentation that have shown promise in drug delivery and tissue engineering applications [46]. Polyanhydrides are surface-eroding biodegradable polymers that degrade primarily from the surface, providing near-zero-order drug release kinetics, and they have been used in FDA approved products such as the Gliadel wafer for local chemotherapy in brain tumors [47]. Polyorthoesters are another class of surface-eroding polymers that are sensitive to acidic conditions, making them suitable for pH triggered drug delivery [48]. Natural biodegradable materials, including proteins such as albumin, silk fibroin, and zein, have been explored as drug delivery matrices due to their inherent biodegradability and biocompatibility [49]. Silk fibroin, derived from the silkworm Bombyx mori, can be processed into a variety of forms including films, hydrogels, microspheres, and nanoparticles, and its degradation

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rate can be tuned by controlling the degree of crystallinity (β-sheet content) [50]. Biodegradable inorganic materials, such as mesoporous silica nanoparticles and calcium phosphate cements, have also been explored for controlled drug delivery, offering high drug loading capacity and Tunable degradation [51]. The degradation products of biodegradable polymers must be non-toxic, non-immunogenic, and readily cleared from the body to ensure safety [52]. In PLGA systems, the autocatalytic effect, where accumulation of acidic degradation products within the matrix accelerates further degradation, can lead to unexpected burst release and must be carefully managed through formulation optimization [53]. Biodegradable materials continue to evolve with the development of new synthetic routes and copolymer designs that offer improved control over degradation kinetics, mechanical properties, and biological interactions [54].

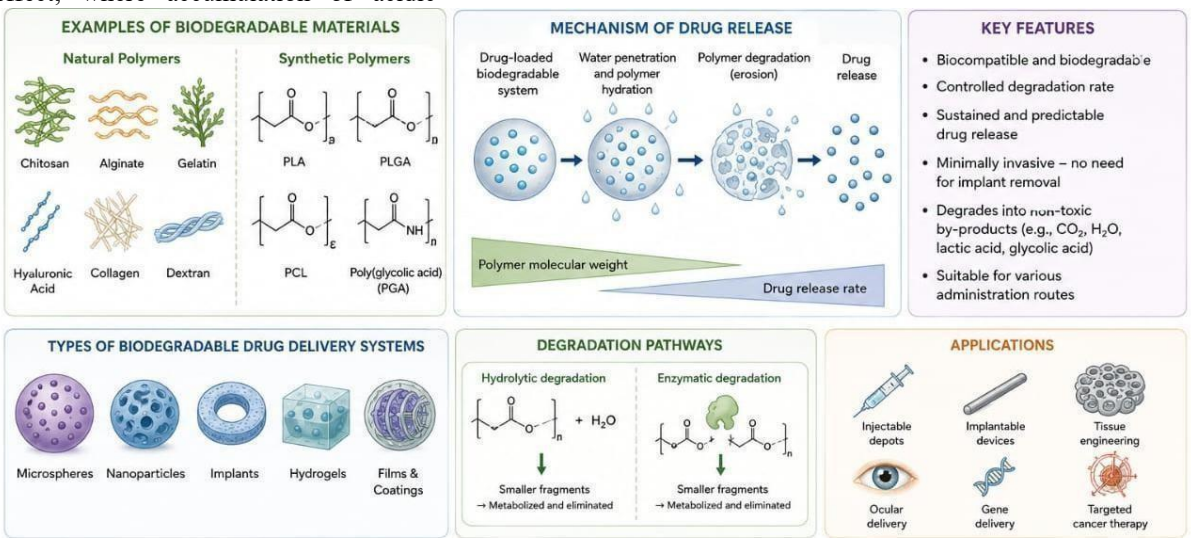

Fig. 2.2 Biodegradable materials

Smart Materials

Smart materials, also referred to as stimuli-responsive or intelligent materials, are designed to undergo significant and reversible changes in their physical, chemical, or mechanical properties in response to specific environmental stimuli [40, 49]. These materials represent the frontier of drug delivery science, enabling the transition from passive controlled release to active, on-demand, and spatiotemporally precise drug delivery [41]. This phase transition is exploited in injectable hydrogel systems that are liquid at room temperature and gel at body temperature, forming in situ drug depots [43]. pH-responsive materials based on polyelectrolytes such as poly (acrylic acid), poly (methacrylic acid), chitosan, and their derivatives can selectively swell or collapse depending on the environmental pH, enabling targeted drug release in specific regions of the gastrointestinal tract or within acidic tumor microenvironments [44, 51]. Dual-responsive and multi-responsive materials that combine sensitivity to two or more stimuli (e.g., pH and temperature, pH and redox, or temperature and enzyme) within a single carrier system offer synergistic control over drug release [45, 52]. Magnetic nanoparticles, typically based on iron oxide, can be incorporated into polymer matrices or liposomes to enable magnetically targeted drug delivery and triggered release through localized hyperthermia under an alternating magnetic field [46]. Photoresponsive materials containing photocleavable groups such as o-nitrobenzyl esters or azobenzene moieties

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can undergo structural changes upon exposure to specific wavelengths of light, providing remote drug release with high spatial and temporal precision [47]. Redox-responsive materials exploit the significant difference in glutathione concentration between the extracellular environment (approximately 2–10 μM) and the intracellular cytoplasm (approximately 2–10 mM), using disulfide bonds as redox-sensitive linkers that are cleaved upon internalization into cells [48]. Glucose-responsive materials, typically incorporating glucose oxidase, phenylboronic acid, or concanavalin A, are designed for self-regulated insulin delivery, where insulin release is triggered by elevated blood glucose levels [49]. Shape-memory polymers are an emerging class of smart materials that can be deformed into a temporary shape and recover their original permanent shape upon application of an appropriate stimulus, with potential applications in self-deploying stents and implantable drug delivery devices [50]. Despite significant progress, the clinical translation of smart materials remains challenging due to the complexity of their synthesis, potential long-term toxicity concerns, regulatory hurdles, and the difficulty of achieving consistent performance in the heterogeneous biological environment [52].

METHODS OF PREPARATION

Direct Compression

Direct compression is the simplest and most cost-effective method for preparing controlled and sustained release matrix tablets, involving the direct compaction of a blend of drug, polymer, and excipients into tablets without any prior granulation step [40, 54]. The process consists of only two primary operations: blending (mixing) the powder ingredients and compressing the blend into tablets using a rotary or single-punch tablet press [41]. The elimination of the granulation step reduces processing time, energy consumption, and manufacturing costs, and avoids exposure of the drug to moisture and heat, making it particularly suitable for thermolabile and moisture sensitive drugs [42]. For direct compression to be successful, the powder blend must possess adequate flow properties, compressibility, and content uniformity [43]. Directly compressible excipients, such as microcrystalline cellulose (Avicel PH 102), spray-dried lactose, dibasic calcium phosphate, and pre-gelatinized starch (Starch 1500), are specifically engineered to have excellent flowability and compactability [44]. In sustained release applications, the drug is typically blended with a rate-controlling polymer such as HPMC (Methocel), ethyl cellulose, or Eudragit, along with fillers, lubricants (magnesium stearate), and glidants (colloidal silicon dioxide) [45].

The compression force applied during tableting influences the tablet hardness, porosity, and consequently the drug release rate from the matrix [46]. Higher compression forces generally produce denser tablets with lower porosity, which can reduce the rate of water penetration and drug diffusion, resulting in slower drug release [47]. However, excessively high compression forces can lead to lamination and capping defects that compromise tablet integrity [48]. The particle size distribution of the powder blend is a critical factor affecting both the uniformity of drug content and the mechanical properties of the compressed tablet [49]. Segregation of particles during blending or transfer can lead to content uniformity failures, particularly when there is a significant difference in particle size between the drug and excipients [50]. Lubricant sensitivity is another important consideration; overblending with magnesium stearate can coat particle surfaces excessively, reducing interparticle bonding and resulting in softer, more friable tablets [51]. Despite its simplicity, direct compression has limitations including its unsuitability for drugs with poor flow properties, low bulk density, or high drug loading requirements where the volume of the tablet becomes impractically large [52]. Advances in excipient technology, including the development of co-processed excipients that combine

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multiple functional properties in a single material, have expanded the applicability of direct compression to a wider range of formulations [53].

Wet Granulation

Wet granulation is the most widely used method for preparing controlled release solid dosage forms, involving the agglomeration of powder particles into granules using a liquid binder solution [40, 55]. The process typically involves four main steps: dry mixing of the drug and excipients, addition of the granulating fluid (binder solution), wet massing to form granules, and drying followed by sizing (screening) of the dried granules [41]. The granulating fluid may be an aqueous solution of a binder such as polyvinylpyrrolidone, hydroxypropyl cellulose, or starch paste, or an organic solvent-based solution for moisture-sensitive drugs [42]. The addition of the binder solution creates liquid bridges between the powder particles, and upon drying, these liquid bridges are replaced by solid bridges that hold the granule together [43]. Wet granulation improves the flow properties, compressibility, and content uniformity of the powder blend, overcoming many of the limitations associated with direct compression [44]. The resulting granules have a more uniform particle size distribution, improved bulk density, and reduced tendency for segregation during subsequent processing steps [45]. High-shear granulation uses an impeller and a chopper in a closed bowl to rapidly mix the powder and distribute the binder solution, producing dense, uniform granules with a narrow size distribution [46]. Fluid bed granulation simultaneously suspends the powder in a stream of air while spraying the binder solution from above, producing lighter, more porous granules with excellent compressibility [47]. For controlled release formulations, the drug can be granulated with the rate-controlling polymer, and the intimate mixing achieved during wet granulation ensures uniform distribution of the polymer around the drug particles [48]. The choice of binder type and concentration significantly affects the granule strength, porosity, and drug release profile of the final tablet [49]. Excessive binder addition can lead to over-granulation, producing hard granules that compress poorly and release drug too slowly [50]. The drying step is critical, as residual moisture content in the granules affects tablet hardness, friability, and stability during storage [51]. Tray drying, fluid bed drying, and microwave-assisted drying are common techniques used to dry the wet granules to the desired moisture content [52]. Despite its versatility, wet granulation involves multiple processing steps, longer manufacturing time, and higher costs compared to direct compression [53]. The exposure of the drug to moisture and heat during granulation and drying can be problematic for hydrolytically unstable or thermally sensitive active pharmaceutical ingredients [54].

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Fig. 2.3 Wet Granulation method

Solvent Evaporation

Solvent evaporation is one of the most commonly employed techniques for the preparation of polymeric microparticles and nanoparticles for controlled drug delivery [40, 56]. The basic principle involves dissolving the polymer and drug in a volatile organic solvent, emulsifying this organic phase in an aqueous continuous phase containing a surfactant, and then evaporating the organic solvent to precipitate the polymer and form solid particles [41]. The most commonly used organic solvents include dichloromethane, chloroform, and ethyl acetate, chosen for their ability to dissolve a wide range of polymers and their relatively low boiling points that facilitate evaporation [42]. In the single emulsion (oil-in-water) method, the drug and polymer are dissolved in the organic solvent, and this solution is emulsified in an aqueous phase containing a stabilizer such as poly (vinyl alcohol) [43]. The organic solvent is then removed by evaporation under reduced pressure or by continuous stirring, causing the polymer to precipitate around the drug and form solidified microspheres or nanospheres [44]. The double emulsion (water-in-oil-in-water) method is used for encapsulating hydrophilic drugs, proteins, and peptides [45]. In this technique, an aqueous solution of the hydrophilic drug is first emulsified in the organic polymer solution to form a primary water-in-oil emulsion, which is then emulsified in an external aqueous phase to form the double emulsion [46]. Particle size can be controlled by adjusting parameters such as the stirring speed, the concentration of the surfactant, the polymer concentration, and the volume ratio of the organic to aqueous phase [47]. Higher stirring speeds and surfactant concentrations generally produce smaller particles with narrower size distributions.

The encapsulation efficiency is influenced by the drug's solubility in the organic and aqueous phases, the polymer concentration, and the rate of solvent removal [49]. Rapid solvent evaporation tends to produce particles with higher encapsulation efficiency because the drug has less time to diffuse out of the forming particles into the aqueous phase [50]. Poly (lactic-co-glycolic acid) and polylactic Acid are the most commonly used polymers in solvent evaporation methods for preparing biodegradable microspheres and nanoparticles for sustained drug release [51]. The porosity and surface morphology of the resulting particles significantly affect the drug release kinetics, with more porous particles exhibiting faster initial release rates [52]. Solvent evaporation is also the foundational technique for preparing

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drug-loaded nanoparticles for targeted cancer therapy, where the resulting nanoparticles can be further surface-modified with targeting ligands or percutaneous endoscopic gastrostomy for enhanced accumulation at tumor sites [53]. A major limitation of the solvent evaporation method is the use of organic solvents, which may leave toxic residues in the final product if not completely removed, necessitating stringent quality control and residual solvent testing in accordance with international council for harmonisation of technical requirements for pharmaceuticals for human use guidelines.

Spray Drying

Spray drying is a rapid, scalable, and continuous manufacturing process used to produce dry powders, microparticles, and nanoparticles for controlled drug delivery [40, 57]. The process involves atomizing a liquid feed (solution, suspension, or emulsion) containing the drug and carrier material into fine droplets, which are rapidly dried by a stream of hot air to produce solid particles [41]. The spray drying process consists of four sequential stages: atomization of the feed into fine droplets, contact between the droplets and the drying gas, evaporation of the solvent and particle formation, and collection of the dried product [42]. Atomization is a critical step that determines the droplet size distribution and, consequently, the particle size of the final product [43]. Different types of atomizers are used, including rotary (wheel) atomizers, two-fluid (pneumatic) nozzles, and ultrasonic nozzles, each producing different droplet size ranges and distributions [44]. The inlet temperature of the drying gas, the feed flow rate, the aspirator rate, and the atomization pressure are the key process parameters that influence the particle size, morphology, moisture content, and yield of the spray-dried product [45]. Higher inlet temperatures result in faster solvent evaporation and can produce particles with a hollow or porous morphology, while lower temperatures may yield denser, more solid particles [46].

In controlled release applications, drugs are co-spray-dried with polymeric carriers such as HPMC, Eudragit, chitosan, or PLGA to produce microencapsulated products with modified release characteristics [47]. Spray drying is also extensively used to prepare amorphous solid dispersions of poorly water-soluble drugs, where the rapid solvent evaporation kinetics trap the drug in an amorphous state within a polymer matrix, dramatically enhancing dissolution rate and oral bioavailability [49]. The scalability of spray drying from laboratory to commercial production is relatively straightforward, and the process can be operated under aseptic conditions for the preparation of sterile products [50]. Nano spray drying technology, using specialized equipment such as the Buchi Nano Spray Dryer B-90, has enabled the production of nanoparticles and submicron particles for advanced drug delivery applications [51]. Limitations of spray drying include the thermal degradation of heat sensitive drugs at high inlet temperatures, the relatively low yield when processing small batch sizes, and the difficulty of encapsulating volatile active ingredients [52]. Co-current spray dryers, where the drying gas flows in the same direction as the atomized droplets, are most commonly used in pharmaceutical applications because the dried particles are exposed to the lowest temperature, minimizing thermal damage [53].

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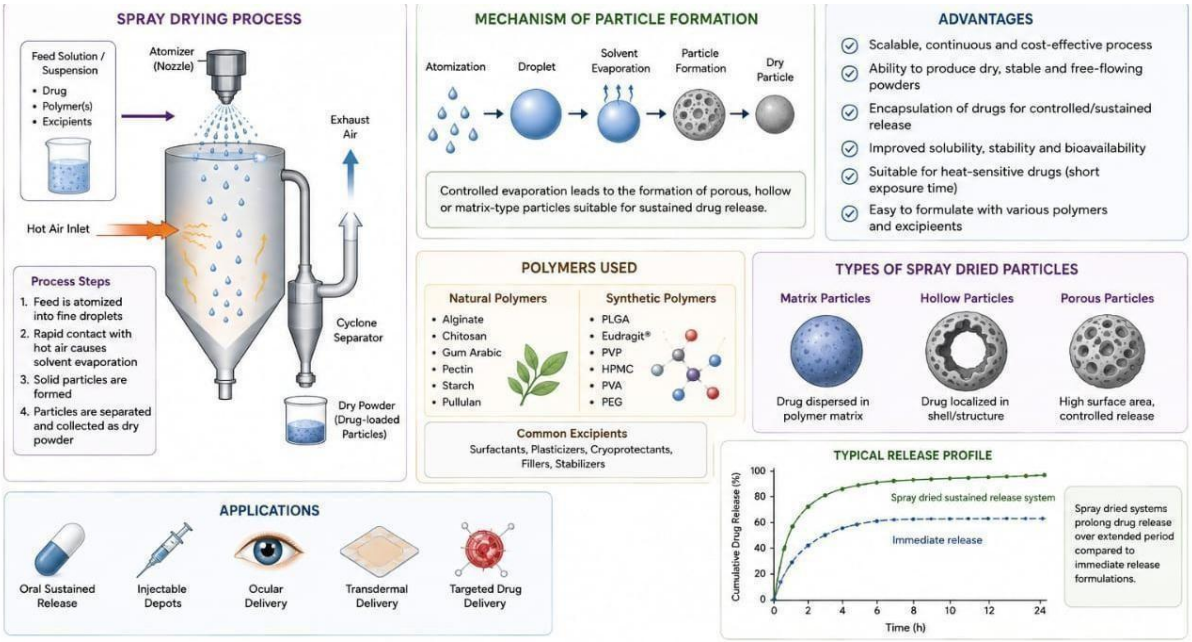

Fig. 2.4 Spray drying

Hot-Melt Extrusion

Hot-melt extrusion is a continuous, solvent-free manufacturing process that has gained significant traction in pharmaceutical applications for producing controlled release dosage forms, amorphous solid dispersions, and medical devices [40, 58]. The process involves feeding a physical mixture of the drug and thermoplastic excipients (polymers, plasticizers, and other additives) into a heated barrel containing one or two rotating screws, where the materials are conveyed, mixed, melted, and extruded through a die of defined shape [41]. Twin-screw extruders are preferred over single-screw designs for pharmaceutical applications because they provide superior mixing, better heat transfer, and self-wiping capability that prevents material degradation from prolonged residence times [42]. The key process parameters in hot-melt extrusion include barrel temperature (zone temperatures), screw speed, feed rate, screw configuration, and die geometry [43]. The barrel temperature must be set above the glass transition temperature or melting point of the carrier polymer to ensure complete melting and homogeneous mixing of the drug within the polymer matrix [44]. Commonly used polymeric carriers in hot-melt extrusion include hydroxypropyl methylcellulose acetate succinate, povidone (Kollidon VA 64), Soluplus, polyethylene oxide, ethyl cellulose, and Eudragit polymers [45]. Plasticizers such as triethyl citrate, polyethylene glycol, and stearic acid are often added to reduce the processing temperature and improve the flexibility of the extrudate [46].

For sustained release applications, the drug is dispersed within a rate-controlling polymer matrix during extrusion, and the resulting extrudate can be cut into tablets, milled into granules, or shaped into films and implants [47]. Hot-melt extrusion is particularly advantageous for preparing amorphous solid dispersions of biopharmaceutics classification system Class II drugs (low solubility, high permeability), as the intense mixing and rapid cooling upon extrusion can effectively convert crystalline drugs to the amorphous state within a stabilizing polymer matrix [48]. The absence of organic solvents eliminates concerns about residual solvents in the final product and reduces environmental impact compared to solvent-based processes [49]. Hot-melt extrusion is a continuous process, which is aligned with the pharmaceutical industry's move

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toward continuous manufacturing and Process Analytical Technology for real-time quality monitoring [50]. In-line and at-line spectroscopic techniques such as near-infrared spectroscopy and Raman spectroscopy can be integrated with the extruder for real-time monitoring of drug crystallinity, content uniformity, and moisture content [51]. Limitations of hot-melt extrusion include the requirement for thermally stable drugs and excipients, the high energy input needed for processing, and the complexity of scaling up the screw design and process parameters [52]. Drugs that degrade at temperatures below the processing temperature of the polymer are not suitable for hot-melt extrusion, and co-processing with suitable plasticizers or the use of lower-melting-point polymers may be necessary to reduce the required processing temperature [53].

Microencapsulation Techniques

Microencapsulation is a process in which small particles or droplets of a drug are coated or enclosed within a polymeric or lipid shell to produce microspheres (matrix-type) or microcapsules (reservoir-type) with particle sizes typically ranging from 1 to 1000 micrometers [40, 59]. The primary objectives of microencapsulation in drug delivery are to protect the drug from degradation, mask unpleasant taste or odour, reduce gastrointestinal irritation, achieve sustained or controlled release, and improve drug targeting [41]. Coacervation (phase separation) is one of the oldest and most widely used microencapsulation techniques, involving the deposition of a polymer-rich phase around the drug particles through changes in temperature, pH, or the addition of a nonsolvent or incompatible polymer [42]. Simple coacervation involves a single polymer, while complex coacervation uses two oppositely charged polymers (e.g., gelatine and gum arabic) that form an interpolymer complex coating around the drug core [43]. Spray drying, as discussed previously, is also a major microencapsulation technique, where the drug core is suspended or dissolved in a polymer solution that is atomized and dried to form coated microparticles [44]. Spray congealing (spray chilling) is a related technique in which a drug is dispersed in a molten wax or lipid, atomized, and cooled to form solid lipid microspheres suitable for sustained release [45]. Fluidized bed coating (Wurster coating) is an industrial microencapsulation method in which drug particles are suspended in an upward stream of air while a coating solution is sprayed onto them from a bottom-spray nozzle, building up a uniform polymer film around each particle [46].

The Wurster process is widely used for taste masking, enteric coating, and sustained release coating of drug particles and pellets [47]. Interfacial polymerization involves the formation of a polymer membrane at the interface between two immiscible phases, where the drug is encapsulated within the core as the membrane forms around it [48]. Ionotropic gelation, commonly used with alginate and chitosan, involves the cross-linking of polyelectrolytes with oppositely charged ions or polymers to form hydrogel microspheres [49]. The choice of microencapsulation technique depends on the physicochemical properties of the drug, the desired particle size, the required release profile, the nature of the coating material, and scalability considerations [50]. Particle size, shell thickness, porosity, and the distribution of drug within the microcapsule are critical parameters that determine the encapsulation efficiency and drug release kinetics [51]. Recent advances in microencapsulation include the use of microfluidic technology to produce highly monodisperse microspheres with precisely controlled size, composition, and architecture [52]. Electrospraying and electrospinning are emerging microencapsulation techniques that use high-voltage electric fields to produce micro- and nanoparticles or fibres with drug-loaded cores and polymer shells [153]. The industrial scale-up of microencapsulation processes remains a significant challenge, requiring

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careful optimization of process parameters to maintain batch-to-batch reproducibility and product quality [54].

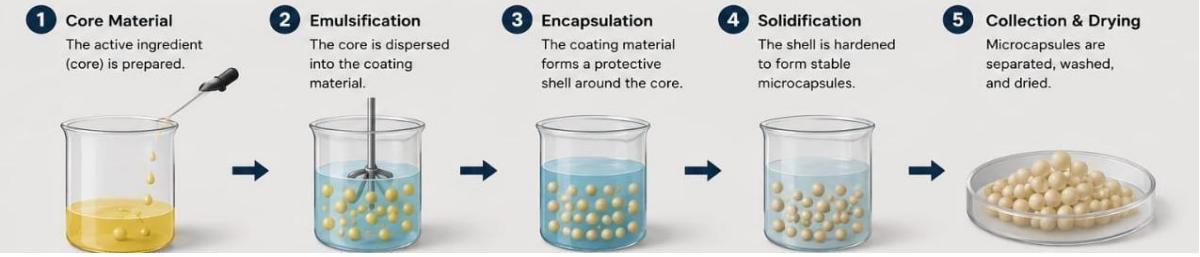

Fig. 2.5 Microencapsulation Technique

Table 1.2 Overview of drug release mechanisms, materials, and preparation methods

Category	Type	Key Mechanism/Feature	Representative Examples	Applications	Reference
Release Mechanism	Diffusion controlled	Fick's laws, concentration gradient driven	HPMC matrices, reservoir membranes	Oral sustained release, transdermal patches	[40, 42]
	Dissolution controlled	Noyes-whitney equation; solubility dependent	Enteric coated tablets, wax matrices	Gastric production, sustained release	[46, 55]
	Erosion-controlled	Surfaceor bulk erosion of Biodegradable	PLGA microspheres, polyanhydride wafers	Implants, injectable depots	[52, 55]
	Osmotic pressure controlled	Osmotic water influx through semipermeable membrane	OROS systems, elementary osmotic Pumps	Zero-order oral delivery	[43, 56]
	Stimuli-responsive	Response to pH, temperature, enzymes, light, magnetic field	PNIPAAm pH-hydrogels, sensitive micelles	Tumor-targeted, on demand release	[47, 49]
Materials	Natural polymers	Biocompatible, enhance lipophilic drug bioavailability	Chitosan, alginate, hyaluronic acid, cellulose	Nanoparticles, hydrogels, coatings	[50, 55]
	Synthetic polymers	Tunable properties, reproducible, FDA-approved	PLGA, PEG, PCI Euagaric, PNIPAAm	Microspheres, nanoparticles, implants	[60, 63]

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	Lipids	Biocompatible, enhance lipophilic drug bioavailability	Liposomes, SLNs, NLCs, SEDDS	Parenteral, Oral	[42, 58]
	Biodegredable materials	Degrade to non-toxic products, no retrieval needed	PLGA, polyanhydrides, MSNs, MOFs	Implants, injectable systems	[53, 58]
	Smart materials	Respond to stimuli, enable on-demand release	Magnetic NPs, gold NPs, SMPs, carbon materials	Tiggered release, theranostics	[59, 67]
Preparation	Direct compression	Simple, cost-effective, no moisture	HPMC matrix tablets	Oral sustained release	[42, 44]
	Wet granulation	Improved flow, content uniformity	Sustained-release granulated tablets	Oral controlled release	[50, 52]
	Solvent evaporation	0/W or W/O/W emulsion, solvent removal	PLGA, microspheres manoparticles	Injectable depots, sustained release	[57, 58]
	Spray drying	Rapid drying, continuous, scalable	Inhalation particles, solid dispersion	Pulmonary, oral delivery	[65, 69]
	Hot-melt extrusion	Solvent-free, continuous, intimate mixing	Matrix tablets, implants, films	Sustained release, amorphous dispersions	[52, 61]

EVALUATION AND CHARACTERIZATION

Drug Content and Uniformity

Drug content and uniformity are essential quality control parameters for controlled and sustained release systems to ensure each dosage unit delivers the intended therapeutic dose [69]. For matrix tablets or multiarticulate, content uniformity testing is typically conducted by assaying individual units against pharmacopoeia standards, such as the United States Pharmacopeia <905> [1]. High-performance liquid chromatography and ultraviolet-visible spectroscopy are the most common analytical methods used to quantify drug loading and verify that the Active Pharmaceutical Ingredient is uniformly distributed within the polymer matrix [70]. Weight variation tests are also performed as a surrogate for uniformity, particularly for tablets, where a low relative standard deviation indicates consistent filling and compression [71]. Non-uniformity in Sustained release systems can lead to catastrophic dose dumping, where the entire drug load is

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released prematurely, causing toxicity or subtherapeutic exposure [72]. In sustained-release pellets, the uniformity of coating thickness is another critical factor that determines the release rate and must be strictly monitored [70]. Research indicates that the drug-to-polymer ratio must be optimized to prevent segregation during the granulation or blending phase, which would compromise content uniformity [73]. Furthermore, assaying the drug content of the finished product confirms that the manufacturing process, such as hot-melt extrusion or spray drying, has not degraded the Active pharmaceutical ingredient [71]. Consistency in drug content ensures that the release kinetics observed in vitro are representative of the entire batch, facilitating predictable clinical outcomes [69]. Regulatory guidelines require these assessments to be documented for all batches to maintain the quality and safety profiles of long-acting formulations [74].

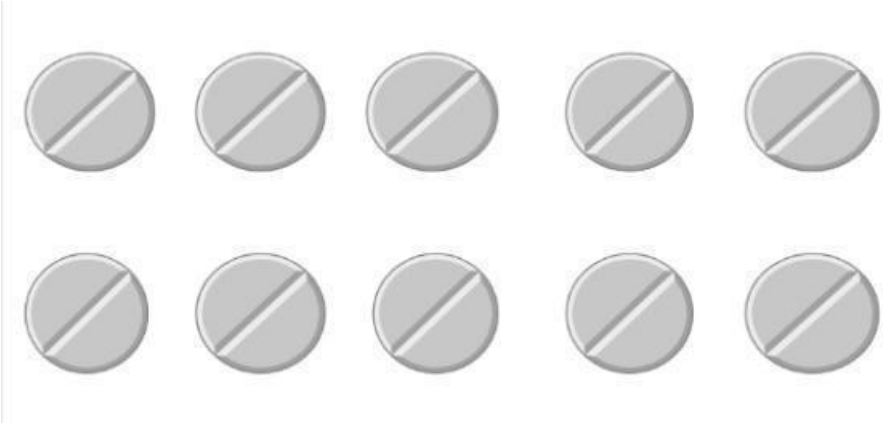

Fig. 2.6 Each tablet contains equal amount of drug

Dissolution Studies

Dissolution studies serve as the primary in vitro characterization tool for evaluating the performance of controlled and sustained release drug delivery systems [71]. These studies are typically conducted using standardized dissolution apparatuses, most commonly Unique Selling Proposition Apparatus I (Basket) for capsules and Apparatus II (Paddle) for matrix tablets [70]. Maintaining sink conditions is a fundamental requirement, ensuring that the concentration of the dissolved drug in the medium does not exceed 10–15% of its saturation solubility [72]. Dissolution media are carefully selected to simulate various physiological environments, such as 0.1 N Hydrochloric acid for gastric simulation or phosphate buffers (pH 6.8 or 7.4) for intestinal release [70]. The sampling intervals for Sustained Release systems are extended over several hours or even days to capture the full release profile and ensure no sudden burst release occurs [74]. Dissolution testing acts as a crucial surrogate for bioavailability, often allowing for the prediction of in vivo behaviour through established in vitro-in vivo correlations [71]. Advanced dissolution methods, such as United States Pharmacopeia Apparatus 4 (Flow-through cell), are increasingly used for sparingly soluble drugs or complex formulations like implants [73]. The cumulative percentage of drug released is plotted against time to generate release profiles that are subsequently analysed using mathematical models [72]. Factors such as agitation speed, temperature (37 ± 0.5°C), and media volume must be strictly controlled to ensure reproducibility and robustness of the data [69]. Ultimately, dissolution testing provides the necessary evidence of controlled release over the intended therapeutic window, guiding the optimization of the formulation [70].

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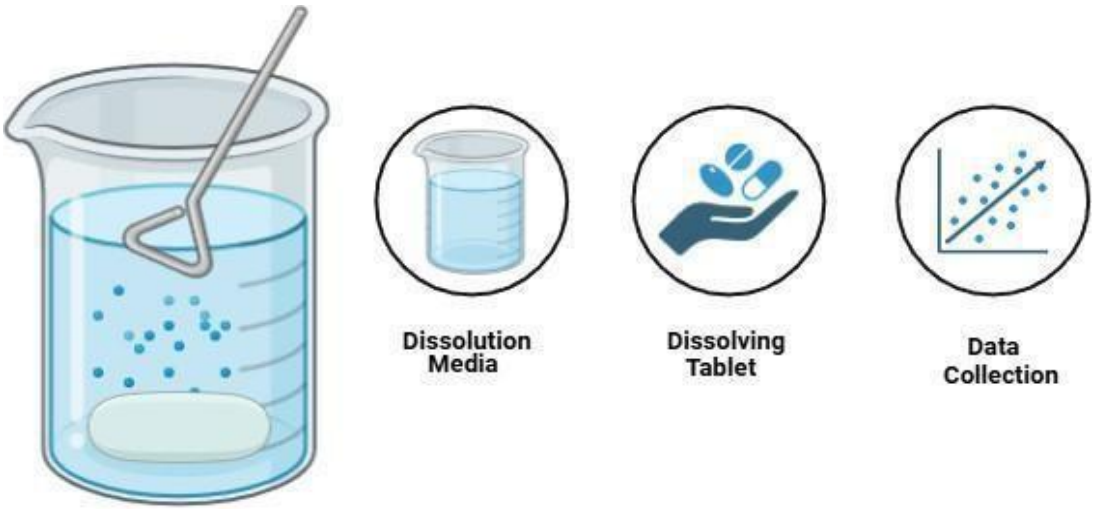

Fig. 2.7 In-vitro Dissolution Study of a Solid Dosage Form

Release Kinetics

The mathematical modelling of drug release kinetics is essential for understanding the mechanisms governing the release of active pharmaceutical ingredients from sustained-release dosage forms [84]. Various kinetic models are used to describe drug release behaviour depending on the formulation and mechanism involved [80]. Zero order kinetics represents systems that release drug at a constant rate, whereas first-order kinetics describes concentration-dependent release profiles [78]. Diffusion controlled systems are commonly explained using the Higuchi model, which relates drug release to the square root of time [75]. In cases where multiple mechanisms such as diffusion and polymer relaxation are involved, the Korsmeyer–Peppas model is widely applied as a semi-empirical approach [76]. These models help in identifying the drug release mechanism and in optimizing formulation performance [80]. Furthermore, kinetic analysis using parameters such as the coefficient of determination allows comparison of different formulations and selection of the most effective drug delivery system [78].

7.1 Zero-Order Release Kinetics

Zero-order release kinetics describes a system in which a constant amount of drug is released per unit time, independent of drug concentration remaining in the dosage form [78]. This model is considered ideal because it maintains steady plasma drug levels and reduces fluctuations associated with conventional dosing [78]. The mathematical expression for zero-order kinetics is $Q_t = Q_0 + k_0 t$, where k_0 is the zero-order release constant [80]. Such behavior is typically observed in systems like osmotic pumps and transdermal delivery systems where release is controlled by device design rather than diffusion alone [84]. However, achieving true zero-order release is difficult in practice due to changes in surface area and drug depletion over time [79]. Despite these challenges, many controlled drug delivery systems are designed to approximate zero-order kinetics to improve therapeutic efficiency [81].

7.2 First-Order Release Kinetics

First-order release kinetics refers to drug release where the rate is proportional to the amount of drug remaining in the system [80]. This results in an exponential decrease in drug release over time [78]. The model is expressed as $\frac{dQ}{} = -kQ$, where k is the first-order rate constant [80]. In such systems, dissolution and diffusion are concentration-dependent processes [79]. Although widely observed, first-order kinetics does not maintain constant

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plasma levels, making it less ideal for controlled delivery applications [84].

7.3 Higuchi Model

The Higuchi model is one of the most important mathematical models for describing drug release from matrix systems and is based on Fiskian diffusion principles [75]. It states that drug release is proportional to the square root of time and is expressed as $Q = k_H\sqrt{t}$ [75]. The model assumes a homogeneous matrix, uniform drug distribution, and negligible swelling or dissolution of the matrix [79]. It is particularly applicable to planar systems such as transdermal patches and matrix tablets [80]. While widely used, the model has limitations when applied to systems involving swelling, erosion, or non-uniform drug distribution [79]. Despite this, it remains a fundamental tool in pharmaceutical research for diffusion-controlled systems [84].

7.4 Korsmeyer–Peppas Model

The Korsmeyer–Peppas model is a semi-empirical equation used to analyse drug release from polymeric systems when the mechanism is complex or not well understood [76]. It is represented as $M_t = kt^n$, exponent indicating the mechanism of drug transport [76]. This model is generally applied to the initial 60% of drug release data [82]. The value of $n$helps classify release mechanisms such as Fiskian diffusion, anomalous transport, and case-II transport [82]. For example, Fiskian diffusion corresponds to lower $n$values, while higher values indicate polymer relaxation-controlled release [83]. This model is widely used for hydrophilic polymer matrices and provides insight into combined diffusion and swelling mechanisms [81]. Although empirical, it is extremely useful when used alongside mechanistic models [84].

STABILITY STUDIES

Stability studies of controlled and sustained release systems are performed in accordance with International Council for Harmonisation guidelines to ensure product quality over time [69]. Accelerated stability testing is typically conducted at 40°C ± 2°C and 75% ± 5% relative humidity to probe the formulation's resistance to environmental stress [71]. Long-term stability studies are carried out at 25°C ± 2°C and 60% ± 5% Relative Humidity, representing the typical storage conditions for Zone II climatic regions [74]. These studies monitor both physical and chemical changes, such as drug degradation, changes in polymer crystallinity, or moisture uptake [72]. In Sustained Release systems, physical stability is particularly important, as any transition in the polymer matrix can drastically alter the dissolution profile and release kinetics [71]. Solid-state characterization techniques, including Differential Scanning Calorimetry and X-ray Diffraction, are used to detect polymorphic transitions during storage [69]. Chemical stability is verified by periodically assaying the drug content and screening for degradation products using validated High-Performance Liquid Chromatography methods [70]. Changes in tablet hardness or friability after storage are also evaluated, as these can affect the mechanical integrity of the sustained-release matrix [75]. The impact of packaging materials, such as blister packs versus high-density polyethylene bottles, is assessed to determine the most protective container-closure system [73]. Successful stability data confirm that the controlled-release mechanism remains intact throughout the product's shelf-life, ensuring patient safety and efficacy [72].

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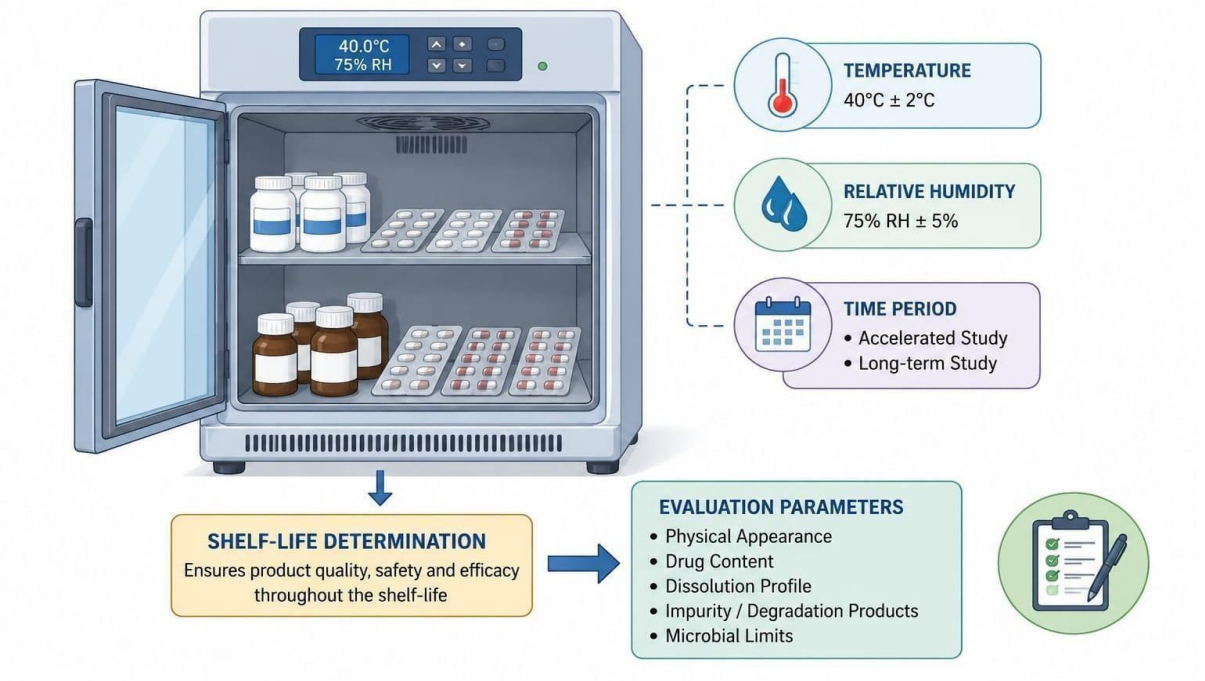

Fig. 2.8 Schematic representation of Stability Testing and Evaluation Parameters

RECENT ADVANCES IN CONTROLLED AND SUSTAINED RELEASE SYSTEMS

Smart Drug Delivery Systems

Smart drug delivery systems are critically important for enhancing therapeutic efficacy and reducing side effects by delivering drugs at the right site, right time, and in the right dose [85]. These systems leverage stimuli responsive carriers that can modulate drug release in response to specific internal or external signals [87, 88]. Internal stimuli include pH changes, enzyme activity, redox potential, and temperature variations often characteristic of disease states like tumors or inflammation. For example, the microenvironment around a solid tumour often exhibits lower pH and higher enzyme concentrations compared to healthy tissues, which can be exploited by pH-sensitive or enzyme-responsive delivery systems to release their payload selectively. External stimuli, such as light, magnetic fields, ultrasound, or electrical signals, offer on-demand control over drug release, providing clinicians with precise temporal and spatial regulation [87]. Polymer-based smart drug delivery systems, particularly those using stimuli-responsive polymers, have shown significant promise for targeted drug delivery and personalized medicine [88, 89]. These systems can achieve controlled release through various mechanisms, including diffusion, dissolution, and erosion, often in combination [91]. The objective is to overcome the limitations of traditional drug delivery, such as frequent dosing and fluctuating drug concentrations, by providing sustained and stable therapeutic levels [91, 92]. Recent advances include hydrogels that swell or shrink in response to changes in pH or temperature, thereby regulating drug expulsion [93].

Nanotechnology-based Delivery

These nanoparticles can be designed to achieve precise drug administration and monitoring, with examples including hyaluronic acid-based nanocarriers for cancer therapy and quantum dots for drug tracking. Surface modification of nanoparticles allows for enhanced drug solubility and targeted delivery, addressing challenges like crossing

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biological barriers and minimizing off-target effects [101,102]. Surface modification of nanoparticles allows for enhanced drug solubility and targeted delivery, addressing challenges like crossing biological barriers and minimizing off-target effects [101,102]. Nanoparticle-based systems are particularly valuable in areas like ocular drug delivery, where anatomical and physiological barriers pose significant challenges for conventional methods [103,104]. They can also be used in transdermal drug delivery systems, combined with physical principles, to achieve real-time control and precise drug release [105]. The development of noisome and polymeric nanoparticles offers advantages such as high drug loading capacity, stability, and reduced toxicity, finding applications in various therapeutic areas including cancer therapy and gene therapy.

3D Printing in Drug Delivery

Three-dimensional printing represents a transformative technology in the pharmaceutical sector, allowing for the fabrication of customized drug delivery systems with precise control over drug release profiles and complex geometries. This additive manufacturing technique enables the production of personalized medicines tailored to individual patient needs, including specific dosages and release rates. The ability of three-dimensional printing to create intricate structures and incorporate multiple active pharmaceutical ingredients into a single dosage form is a key advantage. This technology facilitates the development of multi-layered tablets, matrix systems, and reservoir devices with spatially controlled drug distribution, offering enhanced control over drug release kinetics. For instance, three-dimensional printing can create drug-loaded implants with specific pore sizes and internal architectures, influencing the diffusion and erosion rates of the encapsulated drug. Furthermore, three-dimensional printing can integrate micro/nano-technology into drug delivery systems, enhancing their functionality, such as incorporating nanoparticles or microparticles within printed structures to achieve targeted or sustained release. This innovative approach holds significant potential for revolutionizing the development and manufacturing of controlled and sustained-release formulations, offering improved patient compliance and therapeutic efficacy [90].

Targeted Drug Delivery Systems

Targeted drug delivery systems are designed to concentrate therapeutic agents specifically at the disease site, thereby maximizing efficacy and minimizing adverse effects on healthy tissues [99 -106]. This precision is achieved through various strategies, broadly categorized into passive and active targeting. Passive targeting often exploits unique pathophysiological features of diseased tissues, such as the enhanced permeability and retention effect in tumors, where leaky vasculature and impaired lymphatic drainage allow nanoparticles to accumulate preferentially [98]. Active targeting involves functionalizing drug carriers with specific ligands that recognize and bind to receptors overexpressed on the surface of target cells or tissues [103, 106]. Examples of such ligands include antibodies, peptides, and aptamers [106]. Nanotechnology plays a crucial role in targeted drug delivery, providing versatile platforms like liposomes, polymeric nanoparticles, and inorganic nanoparticles that can be surface-modified for specific recognition [106, 98, 99]. These systems enhance drug solubility and provide controlled release, further optimizing therapeutic outcomes [94, 102]. Targeted delivery is particularly beneficial for treatments like cancer therapy, where selective delivery to malignant cells can reduce systemic toxicity associated with conventional chemotherapy [87, 85]. Recent advancements in targeted drug delivery systems include liposomal, nanoparticle, and vesicular systems that aim for maximal bioavailability and controlled drug release [99].

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Combination Delivery Systems

Combination delivery systems involve the co-delivery of multiple therapeutic agents or the integration of different delivery technologies to achieve enhanced therapeutic effects. This strategy is particularly relevant for complex diseases like cancer, where synergistic effects from multiple drugs can overcome resistance and improve outcomes. For instance, combining L-Asparaginase and Doxorubicin within a single targeted micellar delivery system has shown significant improvement in cytotoxic efficacy against leukaemia cells. This approach allows for the precise co-localization of drugs at the target site, potentially at optimized ratios, which can lead to superior therapeutic benefits compared to administering agents separately [107]. Beyond drug combinations, these systems also encompass the integration of different drug delivery technologies. For example, the use of three dimensions printing can be enhanced by incorporating micro/nano-technology, creating complex structures that facilitate both controlled release and targeted delivery [90]. Stimuli-responsive carriers can be combined with nanotechnology to create "smart" systems that release multiple drugs sequentially or simultaneously in response to specific triggers [106]. Injectable hydrogels, for instance, can be combined with nanohydroxyapatite for bone regeneration, offering controlled release of therapeutic agents [93, 108]. Moreover, tissue-engineered drug delivery vehicles combine biomaterials with living cells or growth factors, creating advanced platforms for localized and sustained therapeutic delivery [109]. sustained therapeutic delivery [109].

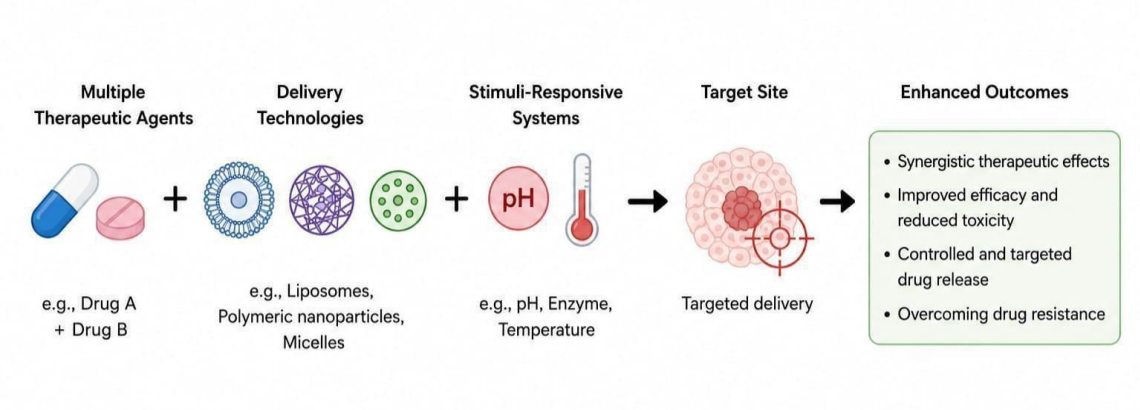

Fig. 2.9 Overview of Stimuli-Responsive Multi-drug Delivery mechanisms

PHARMACEUTICAL APPLICATIONS

Oral Drug Delivery

Oral drug delivery remains the most preferred route due to its ease of administration, patient compliance, and formulation flexibility [110, 111]. However, conventional oral formulations often suffer from poor bioavailability and fluctuations in plasma drug levels, necessitating the development of advanced oral drug delivery systems [92]. Sustained-release matrix tablets represent a significant advancement, providing controlled and prolonged therapeutic effects by regulating drug release over an extended period. These formulations help maintain stable plasma drug concentrations, reduce dosing frequency, and improve patient compliance [112, 113]. Matrix systems, typically composed of hydrophilic, hydrophobic, or inert materials, act as a backbone for modulating release rates [112]. For drugs with short half-lives and high dosing frequencies, extended-release formulations are crucial for achieving therapeutic efficacy [113 -115]. Recent research emphasizes understanding drug properties to design tailored sustained-

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release systems that optimize therapeutic outcomes [114, 115]. Montmorillonite-based sustained release systems are being developed for oral delivery, offering novel approaches to control drug release [116]. The goal is to address issues of toxicity and ineffectiveness that can occur with traditional oral administration methods [111].

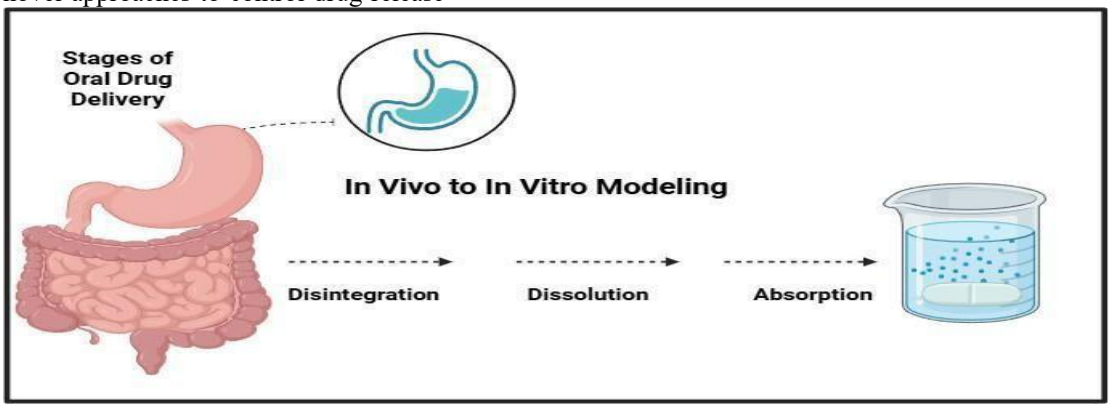

Fig. 3.0 In Vivo to In Vitro Modeling of Drug Delivery

Transdermal Systems

Transdermal drug delivery systems offer a non-invasive route for systemic drug administration, bypassing hepatic first-pass metabolism and providing sustained drug release. Recent advancements in smart physicalbased transdermal drug delivery systems aim for intelligent and controlled release features. These systems combine transdermal technology with novel drug delivery approaches, including nanoparticles, liposomes, and hydrogels, to achieve real-time control and precise drug release. The integration of these components allows for stable, efficient, and safe strategies for drug delivery through the skin [105]. Polymer-based smart drug delivery systems are particularly suitable for skin applications, demonstrating stimuli-responsiveness to various triggers [88, 90]. For example, these systems can be designed to respond to changes in skin temperature or pH, releasing therapeutic agents locally and on demand [88]. Microneedle arrays, often integrated into wearable and implantable technologies, are also emerging as advanced transdermal systems for precise and controlled drug delivery. These innovations contribute to personalized medicine by offering adaptable and responsive transdermal therapeutic options [86].

Injectable Depots

Injectable depots provide a means for sustained drug release over extended periods, reducing the frequency of administration and improving patient adherence [93]. Hydrogel-based injectable systems have gained popularity due to their controlled release, targeted delivery capabilities, and enhanced mechanical properties [93, 108]. These hydrogels hold promise in diverse biomedical applications, including cardiac regeneration, joint diseases, postoperative analgesia, and ocular disorder treatment. The ability to deliver drugs in a controlled manner is crucial for maintaining therapeutic concentrations within the desired window, minimizing fluctuations, and reducing side effects. Injectable hydrogels enriched with nano-hydroxyapatite show particular potential in bone regeneration, addressing challenges related to bone defects, osteoporosis, and tumors-associated regeneration [93]. Furthermore, supramolecular gels, an important category of supramolecules and assemblies, have attracted significant research attention for enhancing drug solubility, retention time, targeting, and stimuli responsiveness in injectable formulations [118]. Silk fibroin, a natural material with excellent biological properties, is also emerging as a

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promising component for the development of novel injectable drug delivery systems due to its versatility in processing and biocompatibility [109].

Implantable System

Implantable drug delivery systems offer long-term, continuous, and localized drug administration, making them ideal for chronic conditions or therapies requiring sustained therapeutic levels. These systems can be designed to release drugs at a constant rate, providing stable plasma concentrations and improving therapeutic efficacy while reducing systemic side effects [86]. Examples include matrix and reservoir systems that utilize biodegradable polymers or rate-limiting membranes to control drug release kinetics [87]. The choice of materials, such as poly (lactic-co-glycolic acid) or silk fibroin, allows for tailored degradation rates and biocompatibility, essential for long-term implantation [109]. Stimuli-responsive implantable devices can release drugs in response to specific physiological changes or external triggers, enabling adaptive therapy. Wearable and implantable technologies, including electrospun Fibers and microchip implants, represent a transformative approach to precision medicine, allowing for continuous monitoring and responsive drug delivery [86]. These implantable systems offer significant advantages in terms of patient compliance and the ability to target specific anatomical sites, such as in ocular or cancer therapies [86, 85, 105].

Ocular and Nasal Delivery

Ocular drug delivery faces unique challenges due to the eye's protective anatomical and physiological barriers, which often result in low drug bioavailability and rapid clearance of conventional formulations [101, 105]. Nanotechnology-based ocular drug delivery systems offer significant advancements by improving drug permeation, enhancing retention time, and enabling targeted delivery to specific ocular tissues [101]. Nanocarriers such as nanoparticles, liposomes, and polymeric micelles are being explored to overcome barriers like the tear film, cornea, and blood-retinal barrier. These systems can achieve sustained drug release, reduce the frequency of administration and improve patient compliance, particularly for chronic eye diseases like glaucoma and macular degeneration [101, 105]. Injectable hydrogels are also gaining interest for ocular disorder treatment, providing controlled and targeted delivery within the eye [93]. For nasal delivery, which offers a non-invasive route to the systemic circulation or directly to the brain, nanotechnology can enhance drug absorption across the nasal mucosa [120]. Micro and nano-carriers are being developed for pulmonary drug delivery, with potential applications for nasal administration by leveraging similar principles of particle size and muco adhesion to optimize drug absorption and retention [120].

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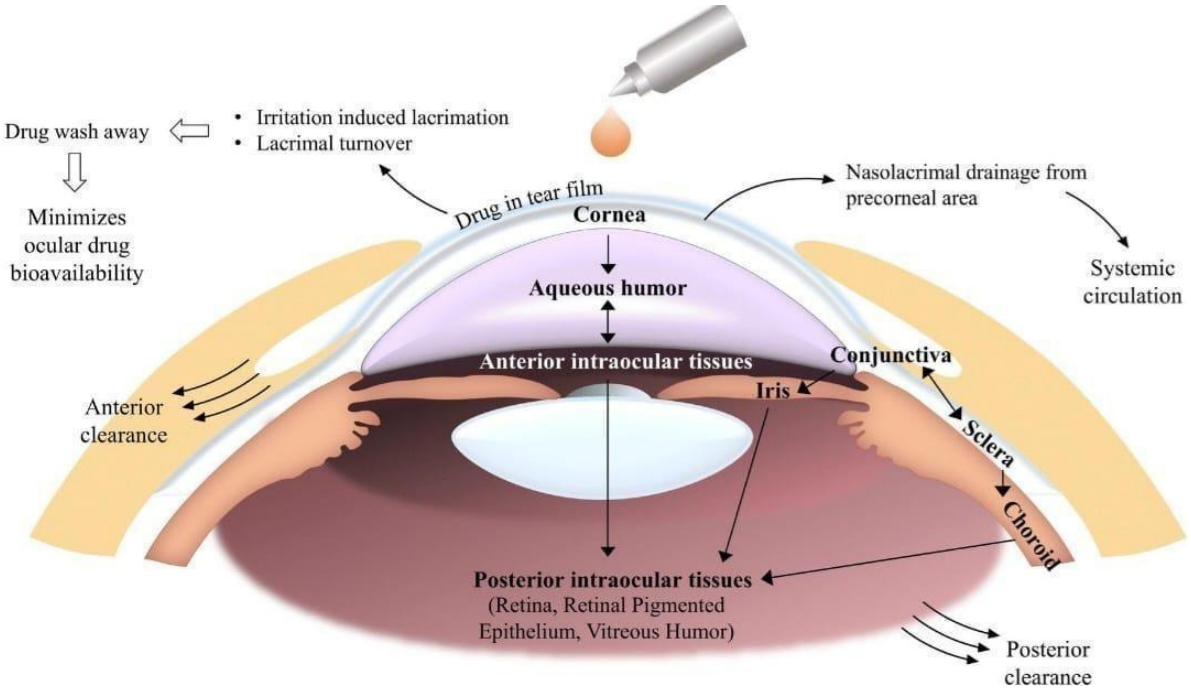

Fig. 3.1 Barriers to Ocular Drug Delivery and Routes of Clearance

ADVANTAGES AND LIMITATIONS

Advantages Reduced Dosing Frequency

The controlled and sustained release formulations are intended to provide extended drug levels to produce the therapeutic effect, which would result in a marked decrease in the number of doses required per day for the patient [121]. Conventional, immediate-release dosage forms may need to be taken two to four times a day, while controlled-release dosage forms may only need to be taken once or twice a day [122]. This decrease in the need for dosing may be especially useful for individuals with chronic conditions like high blood pressure, diabetes and heart or blood vessel disease, who need to take medication for a long time [123]. These drug delivery systems release the drug for a longer period of time, which is either by diffusion, erosion or osmotic pressure. Some of the most common platforms used for once daily dosing are Matrix tablets, reservoir systems, and osmotic pump devices [125]. Sustained release formulations may be used with drugs having short biological half-lives to assure effective plasma levels without frequent redosing [126]. This also makes it easier to manage the care of the patients and decreases the burden on the caregiver in geriatric and paediatric patients [127]. Drug delivery in microparticulate systems and in polymeric implants has been developed to achieve a release that lasts for days, weeks and even months [128]. Depot (microsphere) formulations can yield therapeutic concentrations for 1 month following a single injection [129]. This decrease in the number of doses also helps to reduce the impact on patients' daily routines and schedules [130]. Long-acting formulations have been especially successful for psychiatric disorders where maintaining a steady level of the drug is important for controlling symptoms [131]. Another option for decreasing dosing frequency and maintaining a steady plasma drug level is the transdermal, controlled release patch [132]. The goal of reduction of administration has been further advanced with the development of biodegradable polymeric systems that have been investigated to achieve sustained delivery with zero order release kinetics [133]. Novel delivery systems based on hollow fibers prepared from polylactic acid and

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silk fibroin composites that provide controlled drug delivery for a longer period of time with lower drug dosage have been developed [134].

Improved Patient Compliance

Controlled-release formulation has improved compliance, also referred to as medication adherence, a factor that is one of the most important in determining therapeutic outcomes, with its simplicity of dosing regimens. The number of doses per day has been shown repeatedly to be directly correlated with the amount of non-compliance amongst patients, rendering multiple dose regimens difficult to achieve compared to once-daily doses, which are better in terms of patient cooperation [122]. Controlled-release systems have great advantages for elderly patients who frequently have several medications that need to be taken at the same time [123]. Long-acting injectable formulations have transformed the way psychiatric medicines have been delivered into the world, with their role in maintenance therapy guaranteed to deliver medication to the patient around the clock, irrespective of their behaviour [124]. Oral sustained release products remove the need for patients to take several doses each day [125]. When patients can see that management of their chronic disease is easy and uncomplicated, psychological impacts of such management are lower [126]. Controlled-release systems also minimize the likelihood of missed doses, something that is often a concern with conventional dosage forms that need to be taken several times a day [127]. Sustained release products are especially beneficial to paediatric patients and their caregivers, because they require less frequent exposure to an unpleasant product of the drug [128]. Controlled-release systems lead directly to better clinical results with reduced hospitalisation rates and reduced healthcare cost [129]. Surveys of patient satisfaction have found that people choose the once-a-day formulations over multi-dose-a-day formulations [130]. The development of taste-masked sustained-release formulations has helped to enhance compliance in groups who may be less keen on taking medication [131]. Another compliance benefit of controlled-release transdermal patches is that they deliver the drug in a painless, non-invasive manner and can be managed by patients independently [132]. Smart drug delivery systems with reminder technologies and controlled release mechanisms will be the future of pharmaceutical design that will foster compliance [133].

Controlled Plasma Drug Levels

One of the most pharmacologically important benefits of the controlled-release systems is their capacity of maintaining the plasma drug level in therapeutic range for longer period of time [135]. The conventional immediate release tablets usually generate a peak and a trough in plasma concentrations of the drug, which may lead to toxicity on the peak and sub-therapeutic levels on the trough [136]. Controlled-release formulations are designed to reduce such variability as the body's elimination rate of the drug by releasing the drug at a predetermined rate [137]. Systems that generate zero-order release kinetics, such as osmotic pumps and surface eroding polymers, are those that give the most sustained, constant plasma drug levels. Controlled release systems can also help to keep the drug levels in the body within a narrow therapeutic window, which decreases the likelihood of adverse effects such as those caused by a high concentration of the drug. This is especially significant for drugs with a narrow therapeutic window, such as theophylline, lithium and some antiepileptic drugs [139]. Plasma concentration does not have sharp peaks, which makes the likelihood of acute toxicity events that are observed when drugs are released in bolus form, less likely. The sustained release formulation gives a more uniform pharmacokinetic profile, which is more similar to continuous intravenous infusion [141].

Controlled release systems yield steady-state plasma levels which give more predictable pharmacological responses

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[142]. With the use of the analgesic medications, the controlled plasma level represents consistent pain relief (without breakthrough pain) despite levels of the drug in the body. Antihypertensive controlled release preparations are those that control blood pressure for an entire period of dosing, including the early morning hours [144]. The pharmacokinetic benefits of controlled release have been established by comparative bioavailability studies which have found the peak to trough ratios to be lower [145]. In the case of matrix-based systems with hydrophilic polymers, the near zero order release is assured by the combination of diffusion and polymer swelling [146]. Besides, smart polymers that change their property in response to environmental stimuli like temperature and pH can further regulate the plasma drug levels by changing their release rate in the physiological environment. One of the most basic therapeutic benefits of sustained release is plasma control and it forms the basis of many of the benefits of sustained release formulations in the clinic [147].

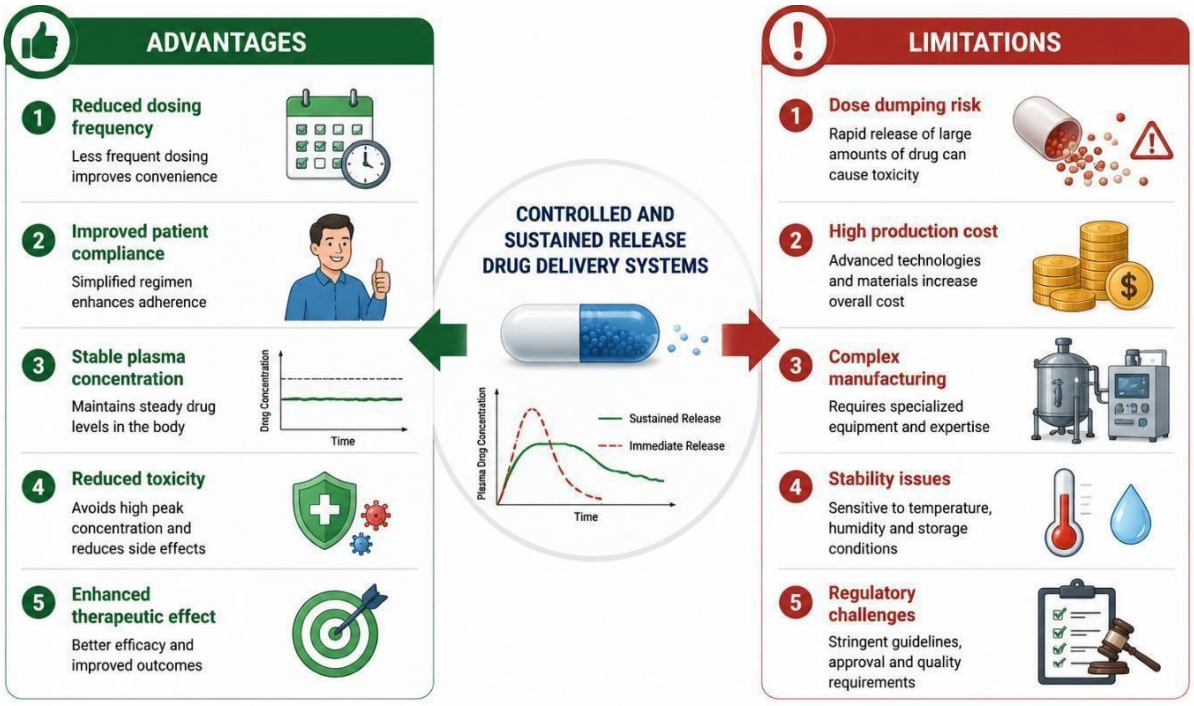

Fig. 3.2 Advantages and Limitations of controlled and sustained release drug delivery systems

Limitations

Dose Dumping Risk

The phenomenon of dose dumping is defined as the sudden and unexpected release of the entire dose of the drug from a controlled-release dosage form, which may result in high plasma drug concentrations and/or adverse drug effects [127]. This may happen as a result of mechanical malfunction of the release-controlling membrane, food or drink, or patient habits (such as crushing or chewing tablets intended for whole consumption) [128]. Drugs with narrow therapeutic indexes are at special risk of severe toxicity or death due to dose dumping because the increase in plasma concentration can be quite toxic [129]. There have been reports of controlled release drug products that have been affected by alcohol induced dose dumping, in which ethanol causes dissolution or alteration of the polymer coating, resulting in an increased drug release [130]. Manufacturers are now required to perform alcohol dose-dumping studies for new controlled-release products to determine this risk [131]. Food and drug administration has

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published some guidance documents on dose-dumping potential in controlled release products. Generally, matrix-type formulations have a lower risk of dose dumping than reservoir-type formulations, where the drug is dispersed in the polymer matrix instead of being contained behind one rate-controlling membrane [132]. A dose dumping effect can, however, be observed for matrix systems where the polymer matrix is affected by environmental conditions [133]. Commonly used technologic approaches to reduce the risk of dose-dumping are the use of abuse-deterrent formulation technologies, multiunit dosage forms, and alcohol- and mechanically-resistant polymer blends [134]. Education of patients on correct administration of controlled release products is crucial to avoid tablet crushing/cutting which can result in a dose dump due to behaviour [135]. The multi-particulate approach in which the total dose is delivered in many smaller doses inherently reduces the dose-dumping risk due to failure of a few doses releasing only a fraction of the total dose [136]. Some formulations are also sensitive to both temperature and dose dumping in extreme storage conditions that affect the properties of the polymers [137]. For controlled release products, it is essential that the Quality Control tests involve a thorough dissolution test in a number of conditions to ensure that potential dose-dumping situations can be identified. One of the most demanding requirements of the controlled release formulation design is to provide for complete drug release during the intended release time without premature release [138].

Complex manufacturing

Production of controlled-release dosage forms is much more complex than that of a conventional immediate release dosage form [140]. Specialized equipment is needed in coating process, pellet layering process, extrusion-spherization process and preparation of microspheres [141]. The manufacturing of osmotic pump tablets involves complex drill to form orifices and even coating the membrane to impart uniformity, necessitating advanced manufacturing capabilities [142]. For combination controlled-release products, multilayer tablet compression technology necessitates special presses and process control [143]. Formulation of microspheres and microparticles for injectable depot formulations is a complex emulsification and evaporation process with multiple critical parameters. The transition from laboratory scale to commercial scale is one of the challenges facing controlled-release systems, as small process changes can have a huge impact on the release profile [144]. Process Control and in-process testing is needed to achieve a uniform coating for Reservoir-Type Controlled Release

Systems [145]. For the preparation of hollow fibre drug delivery systems, the wet spinning technology must be optimized with regard to spinning parameters and polymer concentrations. Controlled release systems can be difficult to manufacture because they may require the use of specialized environmental controls, such as humidity and temperature control, during production [146]. Synthesis of smart polymers that change their properties in response to pH or temperature involve careful control of polymerization conditions. Controlled release products, however, demand more stringent quality assurance than conventional products, which involves dissolution testing at several time points and under several testing conditions [147]. Specialized excipients such as polymers of different grades to control the rate of release further complicates the material sourcing and quality control [148]. For controlled-release systems, it is necessary to have process analytical technology to control critical quality attributes during the manufacturing process [149]. The validation of controlled release manufacturing processes demands a considerable amount of batch-to-batch reproducibility studies in order to guarantee the consistency of the release profiles [150]. There are additional requirements for controlled-release

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products, such as coating thickness, polymer molecular weight, and particle size distribution requirements, which would fall within the auspices of good manufacturing practice requirements [121]. The manufacturing processes for controlled release systems are complex, requiring a skilled work force with special expertise in the field of polymer science and pharmaceutical engineering [122]. Control of drug release from polymer surfaces is available using plasma modification techniques, but these techniques involve an extra step in the manufacturing process and specialized equipment. Multiple technologies in one controlled release product further increases manufacturing complexity [123].

Higher Cost

The costs of controlled-release are not limited to the product itself, but apply to both research and development and distribution, in addition to manufacturing [124]. The special excipients used in controlled release systems, especially the polymers and functional coatings used in pharmaceutical controlled release, are very much higher in cost than the normal excipients used in tablet dosage forms [125]. Controlled release products require significantly more research and development because of the extensive optimization of the formulation, characterization of release kinetics and in vivo pharmacokinetic studies [126]. A significant capital expense with controlled release production is the manufacturing equipment required for controlled release production [127]. In addition to additional testing required for controlled release products, the testing employed is more extensive and time consuming for the more time consuming, leading to higher overall manufacturing costs [128]. For a controlled-release product, the regulatory process is frequently more time consuming and costly, and demands further testing to establish bioequivalence and the absence of a dose-dumping risk. The strategy for patent protection of controlled release technologies frequently includes several patents pertaining to the formulation, manufacturing process, and delivery mechanism, which adds to the cost of Intellectual property protection [129]. Controlled release products must meet more stringent shelf-life stability testing requirements, since the release profiles must be maintained over the product's shelf life [130]. The market price of controlled release formulations is generally higher, due to the greater development and manufacturing expense, and this can make them more difficult for patients in resource limited countries to access [131]. The additional cost of acquisition of the controlled release product should be balanced against the savings in adherence, adverse events, and hospitalizations in health economic analyses [132]. Failure during scale-up of controlled-release manufacturing processes can be costly because of the value of the specialized materials and longer development time [133]. Development cost will be higher for biosimilar and generic products of controlled release products due to the requirement of demonstrating equivalent release profiles and bioequivalence 8. Pharmacoeconomic justification for insurance coverage decisions of controlled release formulation usually involves cost-effectiveness analysis when compared with immediate-release alternatives [134]. The total cost of ownership of controlled-release manufacturing facilities is significantly higher than that of conventional manufacturing facilities, both in terms of maintenance of the specialized equipment and environmentally controlled facility [135]. Although the cost per unit for controlled release may be more expensive, long-term disease management costs may be more favourable [136].

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Table 1.3 Summary of Advantages and Limitations of Controlled and Sustained Release Systems

Category	Aspect	Description	Impact	Reference
Advantage	Reduced dosing frequency	Once or twice daily administration instead of multiple doses	High positive	[121]
Advantage	Improved patient compliance	Simplified regimens increase medication adherence	High positive	[121, 125]
Advantage	Controlled plasma levels	Minimized peak-trough fluctuations within therapeutic window	High positive	[135, 137]
Advantage	Reduced side effects	Lower peak concentrations decrease concentration-dependent toxicity	Moderate positive	[138, 140]
Advantage	Enhanced bioavailability	Prolonged residence time at absorption sites improve drug	Moderate positive	[148]
Advantage	Night-time coverage	Extended duration ensures symptom control during sleep	Moderate positive	[122]
Limitation	Dose dumping risk	Sudden release of entire dose causing potential toxicity	High negative	[127, 128]
Limitation	Complex manufacturing	Specialized equipment and processes required	Moderate negative	[140, 141]
Limitation	Higher cost	Increased R&D, manufacturing, and material expenses	Moderate negative	[124, 125]
Limitation	Limited dose flexibility	Cannot easily adjust doses based on clinical response	Moderate negative	[137]
Limitation	Size and swallowing issues	Large tablets may cause dysphagia in some populations	Low negative	[138]

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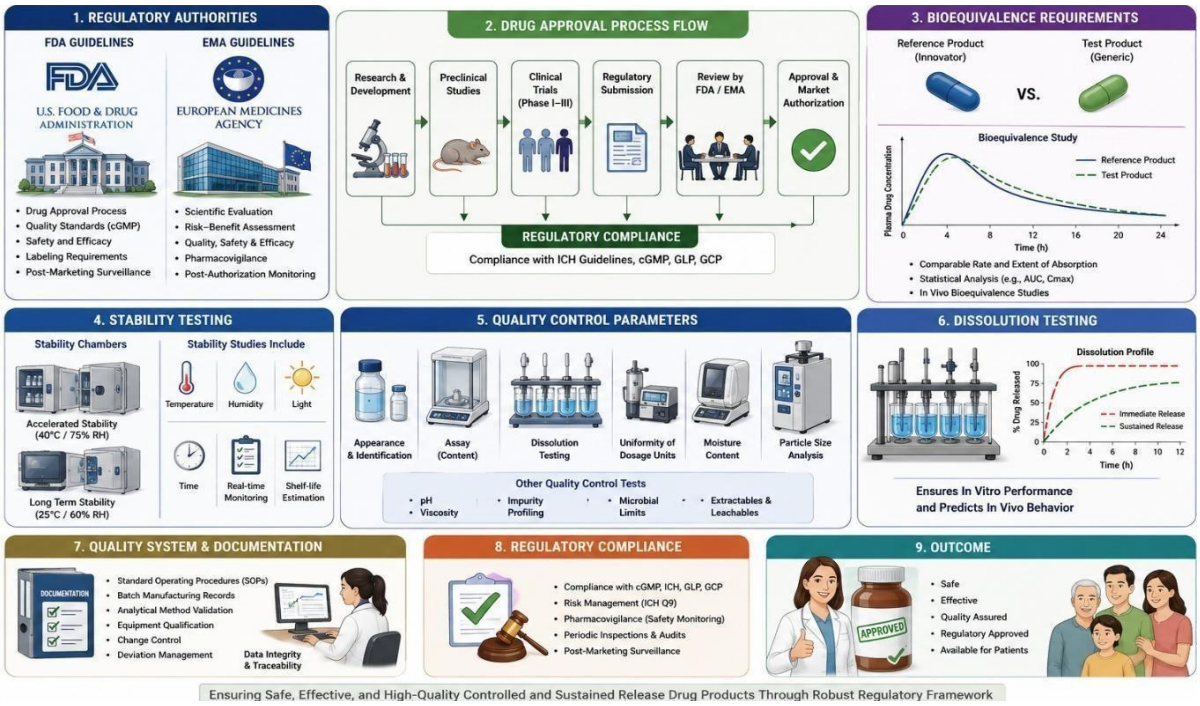

Fig. 3.3 Regulatory considerations for controlled and sustained release drug delivery systems

REGULATORY CONSIDERATIONS

Guidelines (Food and Drug Administration, European Medicines Agency)

The regulatory system for controlled-release products is extensive and complex, with several international regulatory agencies having different but coordinated regulations [121]. Controlled-release drug formulations are regulated by the United States Food and Drug Administration according to the requirements in the Code of Federal Regulations for the manufacturing, testing and approval of modified-release dosage forms. Guidance on the pharmaceutical quality of modified-release products is given in parallel by the Committee for Medicinal Products for Human Use of the European

Medicines Agency [122]. The Food and drug administration's Centre for Drug Evaluation and Research has released certain guidance documents for the development and review of extended-release oral dosage forms [123]. The purpose of these guidance documents is to describe the kinds of studies needed to establish the consistency of the performance of controlled-release pharmaceuticals in different physiological conditions [124]. The Food and Drug Administration requires manufacturers to provide extended dissolution information for the release of controlled-release products in different pH and stirring speeds. The European Medicines Evaluation Agency guidelines indicate that modified-release formulations should show that they work the same way under the expected conditions in the gastrointestinal tract [125]. Comparative bioavailability studies between the controlled release formulation and an immediate release reference product are needed to establish suitable dosage regimen for both agencies [126]. The International Council for Harmonisation gives harmonised guidelines, referenced by the Food and drug administration and European Medicines Agency, for quality, safety and efficacy [127].

Modified-release products are categorized by regulatory agencies as extended-release, delayed-release and controlled-release and have different tests. The route of controlled-release products through the regulatory process is affected by their solubility and

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permeability properties, according to the Food and drug administration's Biopharmaceutics Classification System [129]. There are several pre-market approval pathways, such as the New Drug Application for new drug formulations and Abbreviated New Drug Application for generic drug products [130]. The regulatory process for controlled release device implants includes additional considerations for device safety, biocompatibility and device performance over the long term. The Food and Drug Administration regulations mandate that the drug and device components of implantable drug-device combination products comply with both the drug and device regulatory requirements, which poses a complex approval process [131].

The post-market surveillance obligations for controlled-release products comprise periodic safety update reports, and risk evaluation and mitigation strategies when products have major safety issues. The Guideline on the Quality of Oral Modified Release Products, published by the European Medicines Agency, sets out the needs for pharmaceutical development, manufacturing process validation and control strategy [132]. Prescription drug abuse is a public health crisis, and regulatory agencies have set an increasing demand for the evaluation of abuse deterrent properties of controlled release opioid products [133]. The Food and drug administration has released a draft guidance for industry on the studies required to establish that controlled-release opioids are not abused by typical methods of misuse [134]. Both agencies require extensive stability studies to be conducted to assure that the controlled release process stays stable during the product's shelf life [135]. Pharmaceutical equivalence and bioequivalence to the reference listed drug have to be demonstrated to meet regulatory requirements for generic controlled-release products [136]. The Food and Drug Administration has issued product-specific guidance documents that give guidance on the design of bioequivalence studies for specific controlled-release products [137]. International efforts aimed at harmonizing requirements are on-going, and will bring about harmonization across main markets for the development of controlled release products [138].

Bioequivalence Requirements

Bioequivalence testing of a controlled-release formulation is more complicated than that of an immediate release formulation, because of the characterization of both the rate and extent of absorption of the drug [139]. The Food and drug administration require generic controlled-release products to be bioequivalent to the reference product through meeting statistical criteria for the maximum plasma concentration and area under the plasma concentration-time curve. Controlled-release products might require both single-dose and steady-state bioequivalence studies based on the pharmacokinetics of the drug and the dosage regimen [140]. The 90% confidence interval approach is the most commonly used approach for establishing bioequivalence conditions, which involves ensuring that the confidence intervals of the pharmacokinetic parameters are within the 80– 125% bioequivalence limits of the reference product [141]. Regulatory agencies may consider more stringent bioequivalence requirements for drugs with low therapeutic indices that are formulated as controlled release [142]. Normally, the study design for bioequivalence testing of controlled-release products is a randomized, crossover design with sufficient washout periods between treatments [143]. Oral controlled-release products are typically recommended [144] to have fed and fasted state bioequivalence studies that evaluate the effect of food on the release and absorption of the drug. Dissolution profile comparison is a vital tool in the determination of bioequivalence and the similarity factor (f2) is used to compare the dissolution profiles of the test and the reference products [145]. In vivo Bioequivalence studies can be waived for certain controlled-release products by using the Biopharmaceutics

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Classification System and upon demonstrating that dissolution profile similarity exists [146]. In multiple-unit controlled release dosage forms (e.g., multiarticulate capsules), the bioequivalence requirements may differ from those of single-unit controlled release dosage forms [147]. Controlled release products might need to be analysed using partial area under the curve to achieve the same late exposure profile as the early exposure profile [148]. For controlled release formulations, adequate sampling time points need to be included in the bioequivalence study to ensure appropriate characterization of the absorption phase, peak, and elimination phase [149]. Appropriate study subjects for bioequivalence testing include age, gender, body mass index, and metabolizer status [150].

If the controlled release product is to be administered to special population patients, such as those with altered gastrointestinal physiology, regulatory agencies may require further bioequivalence studies in those patients [121]. For controlled-release products, the concept of in vitro-in vivo correlation is significant since dissolution test can be used as a surrogate for in vivo performance [122]. In vitro-in vivo correlations (in vitro dissolution vs in vivo absorption) are most informative for controlled-release products [123] and represent a point-to-point relationship between in vitro dissolution and in vivo absorption. Additional bioequivalence studies may be needed for post-approval changes in controlled-release formulations, depending on the magnitude of the change in the release mechanism [124]. For complex controlled release products (such as microspheres for injection and transdermal systems), additional parameters are required to satisfy bioequivalence requirements [125]. Bioequivalence guidance is continually revised by regulatory agencies to reflect advances in scientific knowledge of the performance of controlled release products and their clinical effects [126].

Stability and Quality Control

The release profile of a controlled release product should be stable over the shelf life under a variety of storage conditions [127]. According to the International Council for Harmonisation stability guidelines, tests are conducted under long term, intermediate and accelerated conditions [128]. Dissolution testing is the most common quality control method used with controlled release products; specifications are usually established at various points in time to define the release profile. The dissolution conditions such as apparatus type, composition of the medium, and agitation speed should be based on the properties of the drug and the release mechanism of the formulation [129]. Content uniformity, assay, degradation products, and physical attributes are also part of the quality control for controlled release products [130]. Beyond conventional criteria, advanced sustained-release platforms like smart hydrogels, liposomes, and stimuli-responsive nanocarriers present unique degradation pathways that complicate stability profiles. Polymeric matrices, particularly poly (lactic-co-glycolic acid), are highly prone to autocatalytic hydrolysis during storage, which can compromise structural matrix integrity and trigger a premature "burst release" effect [131]. For protein- or peptide-loaded smart delivery systems, physical instability such as aggregation, structural denaturation, or phase separation under environmental stress-remains a persistent hurdle [132]. Consequently, recent formulation strategies increasingly rely on advanced lyophilization techniques and the incorporation of specialized cryoprotectants to maintain the architecture of these nano-formulations over their intended shelf life [133]. In terms of quality control, evaluating complex controlled-release profiles demands a shift from simple dissolution assays to establishing robust In Vitro-In Vivo Correlation frameworks [134]. Modern regulatory pathways, notably enforced by the US FDA and EMA, mandate the integration of Quality by Design principles to evaluate Critical

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Material Attributes and Critical Quality Attributes such as particle size uniformity, surface charge (zeta potential), and encapsulation efficiency [135]. Furthermore, for emerging precision technologies like 3D-printed tablets and microfluidic-tailored carriers, real-time quality monitoring using Process Analytical Technology (PAT) is rapidly transitioning from a premium choice to a mandatory manufacturing standard to eliminate batch-to-batch variability and guarantee therapeutic efficacy [136].

Furthermore, stimuli-responsive drug delivery systems (such as pH, temperature, or magnetic field-triggered matrices) introduce unprecedented challenges to traditional stability protocols. Because these polymers are engineered to undergo structural changes or phase transitions in response to minute environmental triggers, minor fluctuations during standard accelerated stability testing can falsely initiate drug release or polymer degradation [137]. For instance, thermo-responsive hydrogels may undergo premature gel-to-sol transitions if storage temperatures deviate even slightly from specifications, altering the intended sustained-release kinetics permanently [138]. To address this, recent review data suggests that stability protocols for smart therapeutics must incorporate dynamic mechanical thermal analysis (DMTA) and high-sensitivity differential scanning calorimetry (DSC) to accurately map the boundaries of physical stability under realistic environmental stress [139]. From a strict regulatory and quality control standpoint, the characterization of multiarticulate and nanostructured sustained-release dosage forms requires precise analytical validation. Determining the exact mechanism of drug release—whether governed by Fiskian diffusion, polymer swelling, or matrix erosion—is crucial for maintaining regulatory compliance [140]. Current guidelines emphasize the use of mathematical release models (such as the Korsmeyer-Peppas or Higuchi models) as quantitative quality control tools to confirm that batch-to-batch release profiles remain statistically identical (f_2 similarity factor testing) [141]. Additionally, ensuring sterility and low endotoxin levels without compromising the delicate structure of degradable implants or lipid-based nanocarriers represents a major manufacturing hurdle. Traditional sterilization methods like autoclaving or gamma irradiation often degrade the sustained-release matrix or cause premature drug leakage [142]. As a result, modern quality control frameworks heavily scrutinize aseptic processing parameters and require the validation of alternative sterilization techniques, such as supercritical carbon dioxide treatment or sterile filtration through microfluidic systems, to guarantee both product safety and therapeutic longevity [143,144].

The stability-indicating analytical procedure should be validated to ensure that the drug content and release properties are not altered with time [131]. Moisture, temperature and light effects on the polymer based controlled-release system need to be carefully assessed during the stability testing period [132]. The release profile of controlled release systems may change as a result of hydrolytic degradation of the polymeric material during storage, for example Poly (lactic-co-glycolic acid). For controlled-release products, important quality attributes that need to be addressed by quality control strategies are the thickness of the coating, the molecular weight of the polymer, and the porosity [133]. Real-time monitoring of critical process parameters in the controlled-release product manufacturing is possible using Process Analytical Technology [134]. The idea of quality by design has gained much ground in the development of controlled-release drug products, focusing on systematic knowledge of formulation and process variables [135]. Regulatory agencies insist that dissolution requirements for controlled release products be defined by using information about bioavailability and clinical performance [136]. For controlled-release products, there is a need for real-time and accelerated

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stability data to support the proposed shelf life and storage conditions. For controlled-release products, there is a need for Realtime and accelerated stability data to support the proposed shelf life and storage conditions [137]. It is essential that batch-to-batch variations in the release rate are within acceptable limits to guarantee the clinical performance [138]. For controlled release formulations, the stability of the drug-polymer interactions should be investigated, because incompatibilities may occur during storage which could impact on drug release [139]. Other tests performed for quality control of controlled-release devices for implant include sterility, endotoxin, particulate matter and mechanical integrity test. The evaluation of controlled-release formulation performance in different climatic zones is another consideration of environmental sustainability in the quality control process [140]. Now, more advanced analytical methods, such as near-infrared spectroscopy and Raman mapping are being applied to the non-destructive quality assessment of controlled-release systems [141]. One of the problems in the field of quality control of controlled-release products is the development of clinically relevant dissolution procedures that mimic in vivo performance [142].

Table 1.4 Regulatory Requirements for Controlled-Release Products by Major Agencies

Regulatory Aspect	Food and drug administration (United States)	European medicines agency (Europe)	ICH (International)	Reference
Primary guideline	21%Codeoffederal regulations Modified Release	Guideline on Quality of Oral Modified Release Products	Q6A Specification	[132]
Bioequivalence Criteria	90% Confidence interval within 80-125% for Cmax and Arra under the curve	90% CI within 80-125% for Cmax and Area under the curve	Harmonized in M9 guideline	[141, 126]
Dissolution testing	Multiple time points, multiple media	Multiple Time points, biorelevant media	Q4B Pharmacopoeia harmonization	[129]
Stability testing	25°C/60% Relative humidity long-term	25°C/60% Relative humidity long-term	Q1A(R2) guidelines	[128, 137]
Food effect Studies	Required for oral products	Required for oral products	Addressed in M9	[144, 139]
Abuse-deterrent Evaluation	Required for opioids	Case-by-case assessment	Not harmonized	[133, 134]
Post-market surveillance	Risk Evaluation and mitigation if needed	Periodic Safety Update Reports	E2C(R2) guidelines	[135]
Device combination products	Dual pathway (drug + device)	Dual pathway (drug + device)	Q4B Pharmacopoeia harmonization	[131]

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Fig. 3.4 Challenges in controlled and sustained release drug delivery systems

CHALLENGES AND FUTURE PERSPECTIVES

Scale-Up Issues

One of the most important challenges in the commercial manufacturing of pharmaceuticals is the translation of controlled-release formulations from the lab to commercial production [121]. Many parameters which are successful on the bench scale must be drastically different in production equipment because of differences in heat transfer, mixing and drying behaviour with the batch size [122]. Reservoir-type controlled-release processes are especially prone to scale-up, since the thickness of the film across the batch needs to be optimized in order to be uniform, and this requires careful control of spray rate, air volume, and product temperature [123]. Scale up of microsphere manufacturing processes is characterized by the need to maintain the particle size distribution and drug loading within each batch and in larger volumes, by orders of magnitude. A problem is encountered in extrusion-spherization processes when trying to obtain a uniform size and density of the pellets at large scale in the production of multiarticulate controlled release systems [125]. Failure to scale up is costly: for commercial scale, each failed batch can be a large loss of materials and manufacturing time [126].

To ensure successful scale-up, a process analytical technology has become essential that allows the monitoring and control of critical process parameters in real-time [127]. The ability to predict the scale-up behaviour by computational fluid dynamic and other modelling methods is gaining popularity and significantly reduces the number of experimental trials needed [128]. Scale-up of hot-melt extrusion processes for controlled-release applications must be carefully managed in order to control the thermal history and residence time distribution [129]. Comprehensive validation studies are expected by regulatory agencies to show process understanding and control at all scales of operation [130]. Moving from batch to continuous manufacturing also provides some potential solutions to some scale up issues, but with its own set of technical complexities. To scale up biodegradable polymer-based systems, it is necessary to keep the molecular weight and

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degradation properties of the polymer the same at larger scale [132]. New controlled release technologies may be limited by the availability of specific raw materials in pharmaceutical grade quantities [133]. It is essential to have interdisciplinary participation between formulation scientists, process engineers, and quality assurance to obtain successful scale-up [134]. Platform technologies with proven scalability are being more broadly embraced by the pharmaceutical industry to accelerate and mitigate risk of development time [135].

Personalized Medicine

Personalized medicine constitutes a paradigm change with regard to pharmaceutical therapy, when compared with the common approach of treating patients with a single therapy for everyone [136]. Controlled-release systems are adapting to the customization of dosing, such as by three-dimensional printing where dosage forms with personalized release profiles can be fabricated [137]. There are also pharmacogenomic variations in the rate of drug metabolism that could have a profound influence on the optimal release rate for a controlled release formulation, necessitating genotype dependent formulation selection [138]. Biomarker-responsive drug delivery systems can be combined with personalized medicine to provide real-time control of drug release to suit the physiological characteristics of the patient [139].

The combination products of multiple drugs or different release rates can be designed as three-dimensional printed tablets with multiple chambers to realize personalized combination products [140]. The gastro-intestinal physiology changes with age requires customized formulation design for both paediatric and geriatric populations, with controlled-release formulation [141]. There are differences in body weight and composition which influence distribution and elimination of drugs, and thus may necessitate individualised release rates to maintain optimal plasma levels [142]. The gastrointestinal transit time and pH in the various disease states may affect the controlled-release performance, necessitating the changes in formulation for any given patient [143]. Companion diagnostics that will help in selecting the controlled release formulation is an emerging opportunity in the personalized medicine area [144]. Smart pills containing sensors could help to give feedback on how and when each pill is released and absorbed into the body, ensuring that each person receives the right dose [145].

The regulations for these controlled release products are still evolving, with the agencies creating new pathways to fit the new dosage forms: personalized controlled release products [146]. Personalized controlled-release formulations can be made using small batches of fluidics manufacturing technologies in point-of-care settings [147]. The economy of personalized controlled release products is not as straightforward as the conventional economy of pharmaceutical manufacturing and new strategies for assessing the cost-effectiveness of these products need to be developed [148]. The individual patient's condition, nutritional state and other drugs used in the patient should be accounted for when formulating a controlled-release therapy regimen for an individual [149]. In the future, the combination of personalized medicine and controlled-release technology will enable more optimized therapeutic results in relation to reduced side effects for the patient [150].

Advanced Biomaterials

With the emergence of advanced biomaterials, the possibilities of controlled drug delivery have expanded to new dimensions with more and more complex release strategies and biocompatibility [121]. Smart polymers or stimuli-responsive polymers undergo large reversible chemical or physical changes in response to small changes in the surrounding environment, such as changes in pH, temperature, light, and phase changes. Thermoresponsive polymers with lower critical solution

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temperature can change between swollen and collapsed states, thus regulating the release of the drug in response to changes in temperature within its microenvironment [122]. The site-specific drug delivery in the gastrointestinal tract to different parts of the gastrointestinal tract with different pH because of the pH responsive materials is especially useful for oral controlled release [123].

The biodegradable polymers like polylactic acid, polyglycolic acid and their co-polymer polymers can be modified to allow for controlled release via surface erosion mechanisms. Because of their excellent biocompatibility, biodegradability and Tunable mechanical properties, silk fibroin-based materials have been identified as promising biomaterials for controlled drug delivery. Polyethylene glycol derivatives are versatile platforms to be used in controlled-release systems, characterized by their hydrophilicity, biocompatibility and non-toxic properties, which are all important for safe drug delivery. Hydrogel controlled release systems can swell in response to changes in their environment and release drugs thereby offering intelligent drug delivery capabilities [124]. The self-assembling peptide materials provide control of the nanostructures and drug encapsulation at a molecular level [125]. Polyelectrolyte capsules that are built up layer by layer can be used to release drugs in a programmed fashion by sequential degradation of each layer [126]. A new class of porous materials with outstanding drug loading capacity and Tunable drug release properties are the metal-organic frameworks [127]. Unique properties of carbon-based nanomaterials, such as graphene oxide and carbon nanotubes, such as their high surface area and photothermal responsiveness, can be applied to controlled release of drugs [128]. A controlled release is achieved by controlling the pore structure of ceramic materials; for this purpose, mesoporous silica nanoparticles have been used that can be capped with stimuli-responsive gatekeepers [129]. Chitosan, alginate and cellulose derivatives are some natural polymers that are still being developed for their controlled-release applications as they are abundant, cheap and biodegradable [130]. Biomimetic materials that mimic the biological structures provide new possibilities in the controlled delivery of drugs, where biological interactions are improved [131]. By mixing different biomaterials, a composite material can be produced with synergic properties, which are not possible with a single biomaterial, and can be used to create more complex release profiles [132]. For controlled release, biocompatibility of advanced biomaterials must be taken into consideration in both short- and long-term biological responses. Nanoparticles can be coated with stealth molecules that prevent detection by the immune system, thus prolonging their circulation time and allowing passive targeting. The field of advanced biomaterials for controlled release continues to grow at a rapid rate, and novel biomaterials and design princesses are continually being discovered [133].

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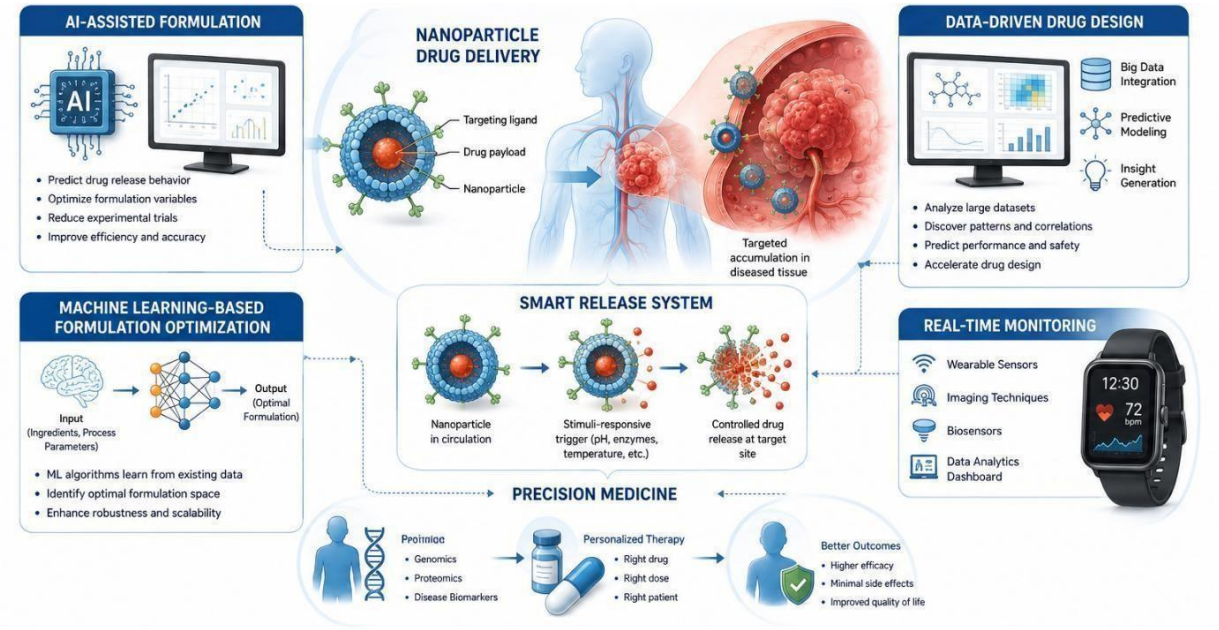

Fig. 3.5 AI and Nanotechnology in controlled drug delivery

The merging of Artificial Intelligence and nanotechnology. The design and optimization of controlled-release drug delivery systems are revolutionized by the use of Artificial Intelligence and machine learning which allows for quick prediction of the formulation performance [134]. Formulation studies can yield vast amounts of data, which can be used to predict the release profile and determine the best formulation using machine learning algorithms, without much experimentation [135]. Incorporating deep learning into the formulation process has been shown to help predict drug-polymer compatibility and release kinetics from molecular descriptors, thereby speeding up the formulation development process [136]. Optimization algorithms based on artificial intelligence can optimize the type, concentration, particle size and manufacturing of the formulation at the same time [137]. Controlled release systems at the nanoscale have been developed, and offer special advantages such as increased cellular uptake and targeted delivery of nanoscale particles [138]. The enhanced permeability and retention effect can be used for passive targeting of tumour tissues by the use of controlled release systems using nanoparticles [139]. Artificial Intelligent and nanotechnology are used together to create a rational design of nanocarriers in terms of their size, shape, surface properties, and release characteristics [140]. Digital twin technology develops virtual versions of controlled-release systems which can simulate their operation when exposed to different physiological conditions [141]. The applications of Natural Language Processing and text mining of scientific literature can help to recognize potential combinations of materials and release mechanisms for designing controlled release materials [142].

Optimization of the sequential decision making associated with multi-step formulation of controlled release products has been suggested using reinforcement learning algorithms [143]. Theranostic systems based on nanotechnology combine the ability to diagnose using imaging techniques with a controlled drug release, allowing monitoring during treatment delivery in real time. Conventional statistical quality control measures are not as fast or accurate in detecting deviations from controlled-release manufacturing processes as are systems of Artificial Intelligence [144]. Using sensors and

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controlled-release delivery system technology allows for the monitoring of a drug's release and patient adherence remotely [145]. Agencies are adjusting their regulatory frameworks to address Artificial Intelligence formulated controlled-release formulations, while regulatory science is evolving to meet the demands of products designed using Artificial Intelligence [146]. The combination of the three technologies (Artificial Intelligent, nanotechnology and controlled-release science) is expected to open a new era of intelligent drug delivery systems that can make autonomous therapeutic decisions [147]. At some point in the future, molecular-level simulation in quantum computing could be used to design controlled-release systems with unprecedented accuracy, by simulating drug-polymer interactions at the molecular level [148]. As Artificial Intelligence becomes more widely adopted in clinical practice, the ethical implications of using Artificial Intelligence for drug delivery, such as transparency and accountability of algorithms, should be explored [149]. The potential of Artificial Intelligent and nanotechnology in controlled drug delivery can only be realized through collaborative research between computer scientists, materials scientists and pharmaceutical scientists.

Table 1.5 Future Technologies in Controlled and Sustained Release Drug Delivery

Technology	Application in Drug Delivery	Current Status	Key Advantage	Reference
3D Printing	Personalized dosage forms with custom release Profiles	Clinical trials	Patient-specific dosing	[137, 140]
Smart polymers	Stimuli-responsive release based on PH/temperature/light	Advanced research	On-demand release control	[122]
AI/Machine learning	Formulation optimization and release prediction	Early implementation	Accelerated development	[135, 136]
Nanoparticles	Targeted controlled release at cellular level	Clinical use (some)	Enhanced targeting	[138, 139]
Digital twins	Virtual modelling of in vivo performance	Research phase	Reduced animal testing	[141]
Self-assembling peptides	Molecular-level drug encapsulation	Preclinical	Precise nanostructure control	[125]
Metal-organic frameworks	High-capacity drug loading with Tunable release	Laboratory	Exceptional loading capacity	[127]
Biodegradable implants	Long-term sustained release (weeks to months)	Food and drug administration approved (several)	Extended duration therapy	[128]
Theranostic nanocarriers	Combined diagnosis and therapy with controlled release	Preclinical/Phase I	Real-time monitoring	[130]
Microfluidics	Point-of-care personalized production	Research phase	Small-batch flexibility	[147]

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CONCLUSION

Recent advances in controlled and sustained drug delivery systems have significantly improved the effectiveness and safety of pharmaceutical therapies by enabling precise, prolonged, and targeted drug release. The development of nanocarriers, smart polymers, stimuli-responsive systems, liposomes, and biodegradable implants have expanded the potential of modern therapeutics for both acute and chronic diseases. Emerging technologies such as exosome-based delivery, 3 dimensions printing, microfluidics, and artificial intelligence-assisted formulation design are further enhancing the customization and efficiency of drug delivery platforms. These innovations contribute to improved bioavailability, reduced dosing frequency, minimized side effects, and enhanced patient adherence. Despite these advancements, challenges including scalability, regulatory approval, toxicity concerns, stability issues, and high production costs continue to limit widespread clinical application. Future research should focus on improving biocompatibility, achieving precise targeting, and facilitating successful clinical translation through interdisciplinary collaboration. Overall, controlled and sustained drug delivery systems represent a rapidly evolving field with immense potential to revolutionize personalized medicine and improve global healthcare outcomes.

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