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Controlled and Sustained Drug Release Using Advanced Polymeric Systems: Formulation Design and Recent Pharmaceutical Applications

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ABSTRACT

Polymer-based controlled- and sustained-release drug delivery systems have become the mainstay of modern pharmaceutical development, offering the ability to maintain therapeutically effective drug concentrations for prolonged periods, reduce dosing frequency, improve patient adherence and, in many cases, lower peak-related toxicity. Fundamental principles of controlled and sustained release are outlined together with the physical mechanisms that govern drug release from polymeric matrices, reservoirs, particulate systems, hydrogels, osmotic devices and implants. Natural, synthetic, biodegradable, non-biodegradable and stimuli-responsive polymers are surveyed with their principal characteristics and release-controlling roles, and formulation strategies including matrix and reservoir designs, coated multiparticulate systems, ion-exchange resins, osmotic pumps, polymeric microspheres and nanoparticles, hydrogels, and long-acting implants are examined. Mathematical models used to describe polymeric drug release — zero-order, first-order, Higuchi, Korsmeyer–Peppas, Hixson–Crowell and Weibull — are summarised, together with the characterisation workflow that supports formulation development. Recent pharmaceutical applications across oral, injectable, transdermal, ocular, implantable, pulmonary and anticancer routes are discussed. The review closes with a critical assessment of the practical advantages, limitations and future directions of polymeric controlled-release technology, including stimuli-responsive smart polymers, three-dimensional-printed dosage forms and long-acting implants for chronic disease management.

Keywords: Controlled release; Sustained release; Polymeric drug delivery; Matrix tablets; PLGA microspheres; Hydrogels; Osmotic pumps; Zero-order kinetics; Biodegradable polymers.

1. INTRODUCTION

Conventional immediate-release dosage forms deliver their entire dose over a short period, producing a sharp rise in plasma drug concentration followed by an equally rapid decline. This pattern is well suited to drugs used for acute symptomatic relief but is a poor match for chronic conditions such as hypertension, diabetes, epilepsy, cardiovascular disease, HIV and many oncological indications, where a sustained, near-steady-state plasma concentration is preferable both for efficacy and for tolerability [1][2]. The consequences of oscillating plasma levels — transient peaks that exceed the toxic threshold, troughs that fall below the

therapeutic minimum, and multiple daily doses that erode patient adherence — have driven several decades of development of controlled- and sustained-release dosage forms in which the rate, time or location of drug release is dictated by the design of the dosage form rather than by patient behaviour or the physiology of the absorption site [3][4].

Polymers are the enabling materials of modern controlled release. Natural polymers such as chitosan, alginate, hyaluronic acid, starch and gelatin, and synthetic polymers such as hydroxypropyl methylcellulose (HPMC), ethylcellulose, poly(vinyl alcohol), polyacrylates, poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(caprolactone) (PCL) and polyethylene glycol (PEG) provide a broad palette of degradation behaviours, mechanical properties, permeability characteristics and stimulus responsiveness that can be exploited to obtain almost any desired release profile [5][6][7].

The pharmaceutical applications of these advances are correspondingly diverse. In oral delivery, hydrophilic and hydrophobic polymer matrices, coated multiparticulates and osmotic tablets provide once-daily or twice-daily formulations of drugs that would otherwise require multiple daily doses [8][9][10]. In injectable delivery, PLGA and related polyester microspheres and in-situ forming implants support long-acting depots that release peptides, hormones and small molecules over weeks to months [11][12][13]. Transdermal patches use polymeric reservoir or matrix designs to sustain systemic delivery for periods of days [14]; hydrogels enable localised, injectable and stimuli-responsive drug release for oncology, wound healing and tissue engineering [15][16]; and long-acting polymer implants are used in contraception, ophthalmology and neurodegenerative disease. The clinical and commercial impact of these systems is substantial: several of the highest-selling brands of the past decade rely on controlled-release polymer technology, and the modernisation of long-acting antiretroviral, antipsychotic and hormonal therapies depend on it.

This review synthesises the 2011–2022 literature on controlled- and sustained-release polymeric systems, with a practical focus on formulation design and recent pharmaceutical applications. Section 2 sets out the fundamentals of controlled and sustained release; Section 3 reviews the polymers used in these systems; Section 4 provides a year-wise synthesis of the recent literature; Section 5 surveys the principal formulation design strategies; Section 6 discusses the mechanisms of drug release from polymer systems; Section 7 outlines characterisation approaches; Section 8 reviews recent pharmaceutical applications across major routes of administration; Section 9 weighs the advantages, challenges and future perspectives; and Section 10 concludes.

2. FUNDAMENTALS OF CONTROLLED AND SUSTAINED DRUG RELEASE

The terms-controlled release and sustained release are often used interchangeably in the practical literature but carry distinguishable technical meanings. Sustained release refers to any dosage form that prolongs the release of drug relative to a conventional immediate-release equivalent, without necessarily maintaining a constant release rate. Controlled release refers more strictly to systems that release drug according to a predefined kinetic profile — most commonly zero-order — and that maintain plasma drug concentrations within a defined therapeutic window for a specified duration [1][2][17]. Both categories share the overarching

objective of maintaining plasma drug concentrations within the therapeutic window for longer than an immediate-release dosage form, thereby reducing the dosing frequency, minimising peak-related toxicity and improving patient adherence [3][4].

The design of a polymeric controlled-release system begins with the physicochemical and pharmacokinetic profile of the drug: aqueous solubility, log P, pKa, molecular weight, permeability, therapeutic window, half-life and site of absorption together determine which release profile is desirable and which polymeric platform is likely to achieve it. Drugs with short biological half-lives, moderate to high therapeutic indices and reliable absorption throughout the gastrointestinal tract are among the best candidates for oral controlled release, while drugs with long half-lives, absorption windows restricted to the proximal gastrointestinal tract, or narrow therapeutic indices may be less well suited [1][2]. For injectable and implantable applications, the additional considerations of biodegradability, tolerability at the site of injection, and the required duration of therapy also inform the choice of polymer and dosage form.

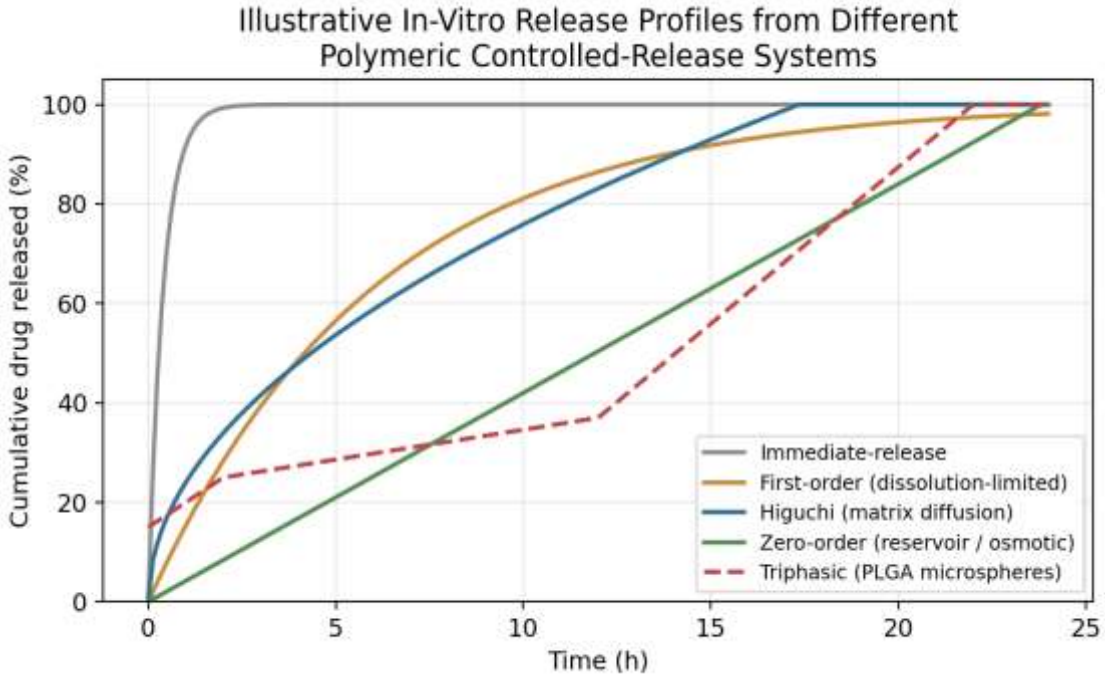


Figure 1. Illustrative in-vitro release profiles from representative polymeric controlled-release systems, generated from schematic kinetic models based on the release patterns commonly reported in the literature.

An ideal controlled-release system in principle exhibits zero-order release, in which the amount of drug released per unit time is constant regardless of the amount remaining in the system. This behaviour maintains a near-constant plasma drug concentration once absorption and elimination reach steady state, and is the theoretical foundation for products such as osmotic tablets and transdermal reservoir patches. In practice, most polymeric systems deviate from strict zero-order release: hydrophilic matrix tablets typically release drug

according to Higuchi kinetics (proportional to the square root of time) or to combined diffusion-and-erosion kinetics described by the Korsmeyer–Peppas equation, and biodegradable microspheres frequently show triphasic release profiles composed of an initial burst, a diffusion-controlled lag phase and a later degradation-driven release phase [4][17][18]. Figure 2 illustrates several of these release patterns.

3. POLYMERS USED IN CONTROLLED-RELEASE SYSTEMS

Natural polymers

Natural polymers used in controlled-release formulations include polysaccharides such as chitosan, alginate, hyaluronic acid, dextran, starch, pectin and guar gum, together with proteins such as gelatin, albumin and collagen. These materials are attractive because they are generally biocompatible, biodegradable, often bioadhesive, and derived from renewable sources; on the other hand, their molecular weight, purity and viscosity can vary substantially between batches, and their release-modulating behaviour is often more difficult to predict than that of well-defined synthetic polymers [5][6]. Chitosan and alginate in particular have been widely used for gastroretentive, mucoadhesive and colon-targeted formulations, exploiting their pH-dependent swelling and dissolution behaviour.

Synthetic polymers

Synthetic polymers dominate contemporary controlled-release formulations because they offer far greater control over molecular weight, composition and functional-group chemistry than natural polymers, and because their long-term safety and biodegradation profiles are well-characterised. Cellulose derivatives — HPMC (hypromellose), hydroxypropyl cellulose (HPC), methylcellulose, ethylcellulose and sodium carboxymethylcellulose — are the workhorses of oral hydrophilic and hydrophobic matrix tablets [8][10]. Polyacrylates (Carbopol, Eudragit), poly(vinyl alcohol) and poly(vinylpyrrolidone) are used both as matrix formers and as coating agents, and Eudragit polymers in particular enable pH-selective release for enteric and colon-targeted formulations. Polyesters — PLA, PLGA and PCL — are the mainstay of injectable and implantable long-acting products [7][11][12].

Biodegradable versus non-biodegradable polymers

Biodegradable polymers such as PLA, PLGA, PCL, poly(anhydrides) and poly(orthoesters) are hydrolysed in the body to non-toxic monomers or oligomers that are cleared via normal metabolic pathways, obviating the need for surgical removal of implanted devices and enabling long-acting depot injections [7][11][12]. Non-biodegradable polymers such as ethylcellulose, silicone rubber and ethylene vinyl acetate (EVA) do not degrade appreciably in vivo but can still be used for controlled release when the device is removed at the end of therapy (for example, transdermal patches and certain ophthalmic and contraceptive implants) or when the polymer serves as a rate-controlling membrane rather than a matrix [14].

Stimuli-responsive and smart polymers

Stimuli-responsive polymers change their physical or chemical properties in response to environmental triggers such as pH, temperature, redox potential, enzymes, magnetic fields, ultrasound or light. Poly(N-isopropylacrylamide) undergoes a reversible sol-gel transition

around 32°C and is widely used in thermosensitive hydrogels; polyacids and polybases with ionisable groups (Carbopol, Eudragit, chitosan) swell or dissolve in response to changes in environmental pH; and disulfide-crosslinked polymers can be selectively cleaved in the reducing intracellular environment of tumour cells [15][16][19]. Smart polymers of this kind provide the technical foundation for on-demand and site-selective controlled release discussed in Section 9.

Table 1 summarises representative polymers used in controlled-release systems together with their principal characteristics and applications.

Table 1. Representative polymers used in controlled- and sustained-release drug delivery systems

Polymer	Category	Key Characteristics	Typical Application
HPMC (hypromellose)	Synthetic, non-biodegradable (in GI transit)	Hydrophilic; forms swollen gel layer; graded by viscosity (K4M, K15M, K100M)	Hydrophilic matrix tablets for oral sustained release [8][10]
Ethylcellulose	Synthetic, non-biodegradable	Hydrophobic; forms diffusion-controlled films/matrices	Film coating, inert matrix tablets [1][14]
Eudragit L/S/RS/RL	Synthetic acrylates	pH-selective or pH-independent release depending on grade	Enteric/colon coatings; controlled-release coatings [6][30]
Carbopol / polyacrylic acid	Synthetic, non-biodegradable	pH-responsive swelling; mucoadhesive	Mucoadhesive tablets, ophthalmic gels [5][28]
Chitosan	Natural polysaccharide	pH-responsive; mucoadhesive; biodegradable	Colon delivery, hydrogels, nanoparticles [5][15]
Alginate	Natural polysaccharide	Ionotropic gelation with Ca^{2+}; pH-sensitive	Gastroretentive tablets, beads, microspheres [5]
PLGA	Synthetic polyester, biodegradable	Bulk-eroding; tunable via MW and LA:GA ratio	Microspheres, nanoparticles, implants [7][11][12]
PCL	Synthetic polyester, biodegradable	Slow degradation (months–years); semi-crystalline	Long-acting implants, scaffolds [6]
PEG / poloxamer	Synthetic	Water-soluble; poloxamers	Hydrogels, coatings,

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		thermosensitive	in-situ forming systems [15][16]
EVA / silicone rubber	Synthetic, non-biodegradable	Permanent matrix; drug diffuses through polymer	Contraceptive & ocular implants; transdermal patches [14][26]

4. LITERATURE REVIEW

Early in the review period, Bruschi [17] provided a widely cited overview of strategies to modify the release of drug from polymeric dosage forms, and Ummadi et al. and Ratnaparkhi and Gupta reviewed the design of sustained-release matrix tablets for oral use [8][9]. Timmins, Pygall and Melia consolidated the historical development and design principles of HPMC hydrophilic matrices, providing a reference framework used extensively in subsequent formulation studies [10]. Around the same period, Fu and Kao reviewed drug release kinetics and transport mechanisms of non-degradable and degradable polymeric delivery systems, providing a mechanistic framework that continues to underpin the field [4].

Studies on polymer particulate systems dominated the review period. Danhier et al. [7] provided an influential overview of PLGA-based nanoparticles for biomedical applications, and Kapoor et al. and Makadia and Siegel described PLGA as a uniquely versatile polymer for controlled drug delivery covering release characteristics from hours to months [12][11]. Anselmo and Mitragotri periodically updated the state of nanoparticles in the clinic during the review period, showing that polymeric nanoparticles and long-acting microspheres constituted a growing share of approved products [20]. In parallel, Kamaly et al. produced a comprehensive review of degradable controlled-release polymers and polymeric nanoparticles, cataloguing the mechanisms by which polymer chemistry controls drug release rate [21].

Studies on hydrogel-controlled release matured particularly rapidly in the second half of the review period. Sood et al. [15] and Li and Mooney [16] reviewed stimuli-responsive hydrogels for drug delivery and tissue engineering, and Kanamala et al. reviewed the mechanisms and biomaterials underlying pH-responsive tumour-targeted drug delivery [22]. Injectable hydrogels for local depot delivery — including thermosensitive chitosan-based systems — became a distinct sub-literature, and stimuli-responsive polymeric nanoparticles for on-demand and targeted release, reviewed by Mura et al. [19] and Karimi et al. [23], moved from proof-of-concept to detailed preclinical evaluation.

Osmotic drug delivery systems, historically dominated by the OROS platform, continued to attract research attention. Comprehensive reviews such as those by Almoshari and Keraliya et al. described elementary, push–pull and controlled-porosity osmotic pumps and their formulation and evaluation [24][25]. Recent primary studies extended osmotic technology to poorly water-soluble drugs (using solubilising excipients or swellable elementary designs) and to ionic-driven osmotic systems, illustrating the continuing evolution of a mature technology.

Toward the end of the review period, additive manufacturing (three-dimensional printing) of controlled-release polymeric dosage forms — enabled by regulatory approval of the first 3D-printed tablet, Spritam, in 2015 — began to attract sustained research and industrial interest, promising personalised release profiles, complex geometries and combination products that are difficult to achieve by conventional manufacture. Long-acting injectable and implantable polymer systems for HIV, contraception, mental health and neurodegenerative disease also became a distinct focus, driven by clinical evidence that adherence-driven benefits of long-acting therapy can substantially improve outcomes [26]. Figure 1 illustrates the overall growth of publications across matrix, implant/microsphere and osmotic polymeric systems during the review period.

Table 4. Year-wise summary of representative polymeric controlled-release literature.

Period	Focus Area	Representative Contribution	Ref.
2011–2013	Consolidation of polymer-based controlled release	Reviews of sustained-release matrix design; PLGA overviews; oral bioadhesive systems	[1][2][7][11]
2013–2014	Hydrophilic matrix and osmotic design	HPMC matrix design principles; osmotic drug delivery reviews; PLGA regulatory research	[9][10][25][13]
2014–2016	Nanomedicine & stimuli-responsive systems	Stimuli-responsive nanocarriers; degradable release-controlling polymers; long-acting injectables	[19][21][26]
2015–2017	Hydrogels & smart polymers	Stimuli-responsive hydrogels; design of hydrogels for controlled delivery; smart nanoparticles	[15][16][23]
2016–2018	pH-responsive & clinical translation	pH-responsive tumour-targeted DDS; nanoparticles in the clinic	[22][20]
2018–2022	3D printing, long-acting implants, osmotic evolution	3D printed tablets; osmotic pump comprehensive review; LAIs for HIV	[32][24][26]

5. FORMULATION DESIGN STRATEGIES

Matrix-based systems

Matrix systems, in which the drug is uniformly dispersed within a polymeric matrix, are the simplest and most widely used oral controlled-release design. Hydrophilic matrix tablets based on HPMC K4M, K15M or K100M are extensively used because HPMC forms a hydrated gel layer on contact with aqueous fluids that controls water penetration into the tablet and drug diffusion out of it; the release rate is modulated by HPMC grade (viscosity), the polymer:drug ratio, drug solubility, tablet hardness and choice of filler [8][9]. Hydrophobic matrix systems based on ethylcellulose, Eudragit RS/RL or waxes such as hydrogenated castor oil release drug primarily by diffusion through inert channels and are typically used for water-soluble drugs. Combinations of hydrophilic and hydrophobic

polymers can extend release beyond what either polymer alone would give and can convert first-order into near-zero-order release [8][10].

Reservoir-based systems

Reservoir systems separate a drug reservoir from the surrounding medium by a rate-controlling polymeric membrane. Under steady-state conditions the release rate is determined by the permeability of the membrane and can be near zero-order for a substantial fraction of the dose. Reservoir designs are used in transdermal patches, in coated pellets and beads for oral use, and in a range of implantable devices. Coating technology (Eudragit RS/RL for pH-independent controlled release, Eudragit L/S for enteric release, ethylcellulose for water-insoluble diffusion barriers) allows precise control over the permeability and thickness of the rate-controlling layer [14][6].

Coated multiparticulate systems

Coated multiparticulate systems — pellets, granules or minitablets coated with a rate-controlling polymer film and filled into hard-gelatin capsules or compressed into rapidly disintegrating tablets — combine the advantages of reservoir release with the flexibility and dose-flexibility of multiparticulate dosage forms. They reduce local irritation, avoid dose dumping (a single unit failing does not compromise the whole dose), and can be blended to give complex, multiphasic release profiles [1][2].

Osmotic drug delivery systems

Osmotic systems exploit osmotic pressure as the driving force for drug release. In the elementary osmotic pump, a tablet core containing drug and osmotically active excipients is coated with a semipermeable membrane and pierced with a laser-drilled orifice; water is drawn in through the membrane by osmosis, the core dissolves, and saturated drug solution is pumped out through the orifice at a rate that is essentially independent of gastric fluid composition and motility, giving near-zero-order release [24][25]. Push–pull, controlled-porosity, sandwiched, telescopic and ionic-driven variants extend the platform to poorly water-soluble drugs and to non-oral applications. Osmotic tablets underpin the widely prescribed OROS product family and are among the most robust of all oral controlled-release designs.

Ion-exchange resin systems

Ion-exchange resin systems reversibly bind the drug to a charged polymeric resin, from which it is released by exchange with counter-ions in the gastrointestinal fluid. The release rate depends on the ionic environment and the affinity of the drug for the resin, allowing sustained release of both cationic and anionic drugs and effective taste masking for pediatric formulations [17].

Polymeric microspheres and nanoparticles

Polymeric microspheres (typically 1–1000 μm) and nanoparticles (typically 10–1000 nm) prepared from PLGA, PLA, PCL, chitosan or alginate are used for injectable and, more recently, for long-acting or targeted delivery. Preparation methods include emulsion–solvent evaporation, nanoprecipitation, coacervation, spray drying and, more recently, microfluidic and electrohydrodynamic techniques [7][11][12]. Release from these particles is influenced

by polymer molecular weight, lactide:glycolide ratio, particle size, drug loading and end-group chemistry, and typically follows a triphasic profile — initial burst, diffusion-controlled lag, and degradation-driven release phase [21]. Figure 4 illustrates how PLGA molecular weight and lactide:glycolide ratio jointly influence the release duration achievable with a PLGA microsphere depot.

Hydrogels and injectable systems

Hydrogels are three-dimensional, hydrophilic polymer networks used for topical, ophthalmic, injectable and implantable controlled release. Chemically crosslinked hydrogels (via covalent bonds) offer good mechanical stability but lack reversibility, while physically crosslinked hydrogels (via ionic interactions, hydrogen bonds or hydrophobic associations) can respond reversibly to environmental stimuli. Injectable thermosensitive hydrogels — most notably those based on poloxamer 407, chitosan/β-glycerophosphate and PEG–PLGA–PEG triblock copolymers — are of particular interest for local depot delivery in oncology, wound healing and post-surgical pain management [15][16].

Long-acting implants

Long-acting polymeric implants deliver drug at controlled rates over weeks to years and are used clinically in contraception, hormone-responsive cancer, ophthalmology and, increasingly, HIV prevention and treatment. They can be biodegradable (PLA/PLGA/PCL rods and pellets) or non-biodegradable (silicone rubber, EVA), and their release characteristics are governed by polymer permeability, degradation rate, and implant geometry [11][26].

Table 2. Principal formulation strategies for polymeric controlled and sustained release.

Formulation Strategy	Working Principle	Typical Release Kinetics	Ref.
Hydrophilic matrix tablet	Drug in swellable polymer; gel layer controls diffusion/erosion	Higuchi / Korsmeyer–Peppas	[8][9][10]
Hydrophobic (inert) matrix	Drug diffuses through inert polymer channels	Higuchi	[1][8]
Reservoir (coated) system	Rate-controlling membrane over drug reservoir/core	Near zero-order	[14][30]
Coated multiparticulate	Rate-controlling film on pellets/minitablets	Reservoir-type; blendable profiles	[1][30]
Osmotic pump (EOP, CPOP, push-pull)	Osmotic pressure drives drug solution through membrane/orifice	Zero-order (typically 60–80% of dose)	[24][25]
Ion-exchange resin	Reversible drug–resin binding released by counter-ion exchange	Sustained; ionic-strength dependent	[17]
Polymeric	Diffusion + polymer	Triphasic (burst,	[7][11][12][21]

microspheres/NPs	degradation	lag, degradation)	
Hydrogel depot / implant	Diffusion + swelling ± degradation	Sustained; often stimuli-responsive	[15][16][31]
Long-acting implant	Diffusion through polymer / degradation of polymer	Near zero-order over months–years	[11][26]

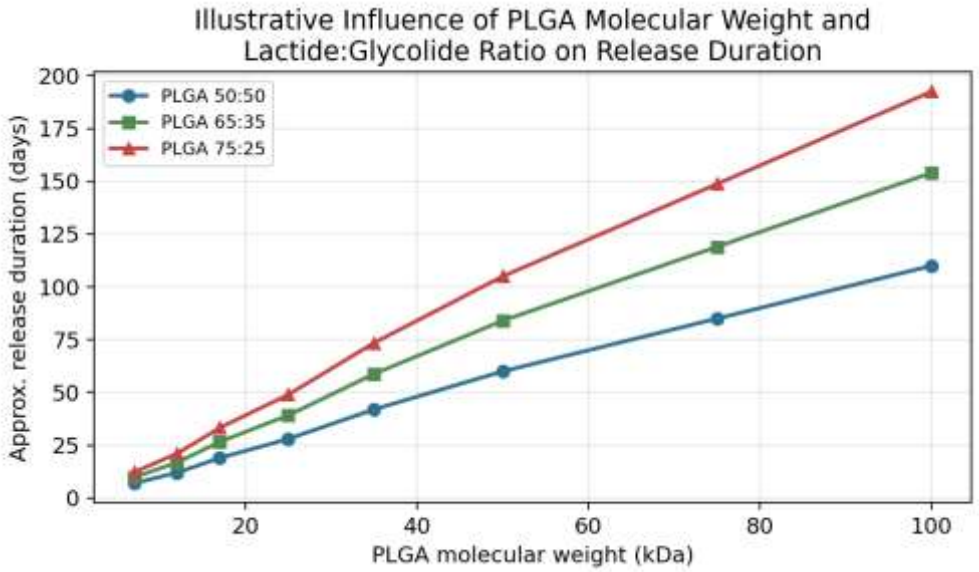


Figure 2. Illustrative influence of PLGA molecular weight and lactide:glycolide ratio on the release duration achievable with PLGA microsphere depots (synthesis of typical ranges reported in the literature).

6. MECHANISMS OF DRUG RELEASE

Diffusion

Diffusion of dissolved drug through a polymer matrix or across a rate-controlling membrane is the dominant release mechanism for most non-degradable polymeric systems and for the early phase of most degradable systems. Fick's laws provide the mathematical framework: in matrix systems dispersing more drug than can be dissolved, release follows the classical Higuchi treatment (proportional to the square root of time) [4][21][27]; in reservoir systems at steady state, diffusion across the rate-controlling membrane gives near-zero-order release. The diffusion coefficient, and therefore the release rate, is influenced by polymer chain mobility, degree of crystallinity and any interactions (hydrogen bonding, electrostatic association) between drug and polymer; formulation choices such as plasticiser content and drug-loading level therefore directly affect release even when the release mechanism itself remains diffusive [4][27].

Swelling

For hydrophilic polymers such as HPMC and crosslinked hydrogels, water uptake swells the polymer network and enlarges its mesh, converting a previously glassy region into a hydrated gel through which drug diffuses. Release from swelling-controlled matrices can approximate

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zero-order kinetics because the advancing swelling front slows drug egress from the increasingly hydrated matrix, partially offsetting the concentration-gradient decline that would otherwise cause first-order behaviour [10][21]. Figure 3 illustrates the effect of increasing HPMC K4M concentration on the sustained-release profile of a model drug.

Polymer degradation and erosion

Biodegradable polymers release drug not only by diffusion but also as the polymer matrix itself is hydrolysed. PLGA undergoes so-called bulk erosion at the dimensional scales typical of microspheres and nanoparticles, resulting in the characteristic triphasic release profile of initial burst, diffusion-controlled lag and later degradation-driven release [11][12][21][27]. Surface-eroding polymers such as polyanhydrides degrade from the outside in and can maintain more constant release rates over long periods, though their processing constraints have limited their commercial adoption relative to PLGA.

Osmotic pressure

Osmotic systems release drug in response to osmotic pressure generated within the dosage form. Because osmotic pressure is proportional to the concentration of osmotically active solutes in the core rather than to the drug concentration itself, osmotic pumps can maintain essentially constant release rates for a large fraction of the dose, giving one of the closest practical approximations to true zero-order release available in oral dosage forms [24][25].

Ion exchange

In ion-exchange resin systems, release rate is determined by the exchange of drug with counter-ions in gastrointestinal fluid, with the exchange rate depending on the resin capacity, drug affinity for the resin, and local ionic environment. This mechanism gives modestly sustained release that adapts partially to the local ionic environment and is particularly useful for taste-masking of ionisable drugs [17].

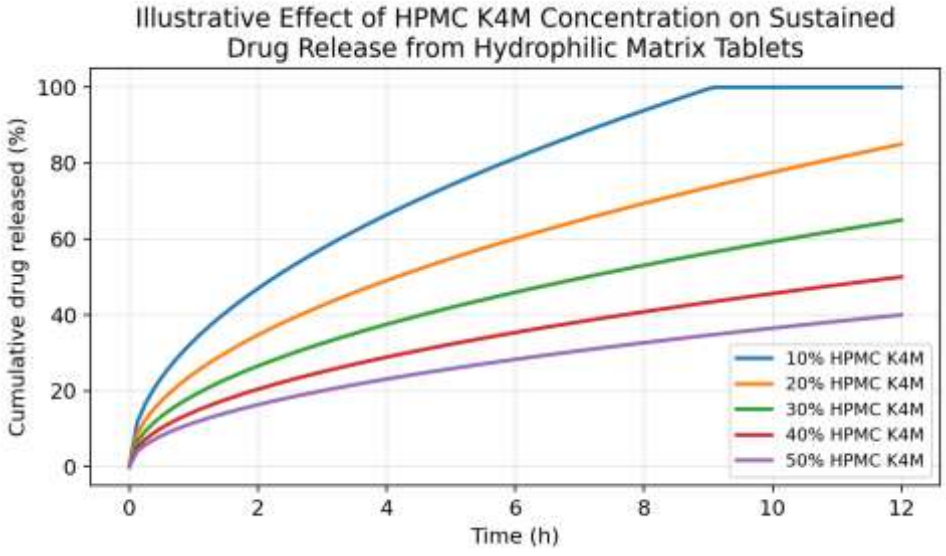


Figure 3. Illustrative effect of HPMC K4M concentration on the sustained-release profile of a model drug from a hydrophilic matrix tablet (illustrative representation of the trends widely reported for HPMC matrices).

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Stimuli-triggered release

Stimuli-responsive polymeric systems couple drug release to a specific environmental change: acidic tumour pH triggers protonation, swelling or destabilisation of pH-responsive polymers; local temperature above the polymer's lower critical solution temperature triggers thermosensitive sol–gel transitions; elevated intracellular glutathione cleaves disulfide crosslinks; and externally applied light, ultrasound or magnetic fields can trigger release at operator-defined times and locations [15][16].

Table 3. Mathematical models commonly used to describe polymeric controlled drug release.

Model	Equation (schematic)	Interpretation / Best-fit Systems
Zero-order	$Q = k_0 \cdot t$	Constant release rate; reservoir, osmotic, some transdermal
First-order	$\ln(Q) = \ln(Q_0) - k \cdot t$	Rate ∝ remaining drug; solution formulations, some matrices
Higuchi	$Q = kH \cdot \sqrt{t}$	Matrix diffusion; hydrophilic/hydrophobic matrix tablets
Korsmeyer–Peppas	$Q/Q\infty = k \cdot t^n$	Diagnostic for Fickian (n≈0.45), anomalous or Case-II release from polymer matrices
Hixson–Crowell	$Q_0^{(1/3)} - Q_t^{(1/3)} = k \cdot t$	Dissolution-controlled release from eroding tablets
Weibull	$Q/Q\infty = 1 - \exp[-(t/T)^b]$	Empirical, flexible; complex biphasic/triphasic release

7. CHARACTERISATION AND EVALUATION

Formulation development for a polymeric controlled-release system typically proceeds through several linked phases. Preformulation characterises the physicochemical and biopharmaceutical properties of the drug — solubility, log P, pKa, permeability, chemical stability and compatibility with candidate polymers and excipients — and thereby narrows the field of feasible polymer platforms and release profiles [1][2]. Formulation optimisation, increasingly guided by Quality by Design and Design of Experiments methodology, then defines the effect of key formulation and process variables (polymer grade and level, drug loading, granulation and compression parameters, coating thickness) on the critical quality attributes of the finished product [17].

Physical characterisation of polymeric tablets and multiparticulates includes weight variation, thickness, hardness, friability, disintegration, content uniformity and porosity (for tablets); particle size distribution, morphology (SEM), surface charge and encapsulation efficiency (for microspheres and nanoparticles); and swelling and erosion behaviour (for hydrophilic matrices). Thermal analysis by differential scanning calorimetry and X-ray diffraction

identify drug–polymer interactions and the physical state of the drug in the matrix. In vitro release is evaluated using compendial dissolution apparatus, flow-through cells, USP Apparatus 4, or sample-and-separate techniques, with release data typically fitted to the family of mathematical models summarised in Table 3 to elucidate the underlying release mechanism [4][17][21][27]. For long-acting parenteral products with release durations from weeks to months, biorelevant in vitro release methods using accelerated conditions (elevated temperature, buffered surfactant media, or agitated flow systems) are used to shorten the practical duration of the test while preserving discriminating power [12].

In vivo evaluation typically progresses from pharmacokinetic studies in rodents (relative bioavailability, sustained-release AUC and Cmax versus immediate-release reference) to bioequivalence-type studies against a suitable reference product. In vitro–in vivo correlation (IVIVC), particularly for hydrophilic matrix and osmotic systems, is a well-established regulatory tool for supporting biowaivers and formulation changes, though establishing a robust IVIVC for complex polymeric systems remains one of the more demanding aspects of controlled-release product development [1][2].

8. RECENT PHARMACEUTICAL APPLICATIONS

Oral controlled and sustained release

Oral delivery remains the largest single application of polymeric controlled release. HPMC-based matrix tablets are extensively used for once- or twice-daily formulations of antihypertensives, antidiabetics, non-steroidal anti-inflammatory drugs, antiretrovirals and central-nervous-system drugs [8][9][10]. Coated multiparticulate systems (pellets and minitablets) are widely used for proton-pump inhibitors and for opioid analgesics where dose dumping must be avoided. Osmotic tablets underpin the OROS product family for antihypertensives (e.g., nifedipine), stimulants and antipsychotics, providing among the most reproducible near-zero-order oral release available today [24][25]. Gastroretentive floating, expandable and mucoadhesive polymeric systems have been developed to extend the residence time of drugs with narrow absorption windows in the proximal gastrointestinal tract. Beyond the well-established antihypertensive and antipsychotic classes, more recent applications include controlled-release formulations of antiretrovirals to extend dosing intervals in resource-limited settings, sustained-release opioid formulations engineered with abuse-deterrent polymer combinations that resist crushing and solvent extraction, and colon-targeted formulations based on Eudragit L and S coatings or on polysaccharides selectively degraded by colonic microflora for the local treatment of inflammatory bowel disease [30].

Injectable controlled release

Long-acting injectable products based on PLGA and related biodegradable polymers dominate parenteral controlled release. Leuprolide-containing PLGA microspheres (Lupron Depot) established the platform for hormone-responsive cancer and endometriosis; risperidone microspheres and octreotide microparticles further extended it to psychiatry and neuroendocrine tumours [11][12]. In-situ forming polymeric implants (Atrigel and similar platforms) provide an alternative approach in which a polymer solution is injected as a liquid that precipitates into a solid depot in situ, avoiding the manufacturing complexity of

preformed microspheres. Over the review period, the injectable long-acting platform expanded significantly into new therapeutic areas: three-month paliperidone palmitate suspensions for schizophrenia, once-yearly zoledronic acid formulations for osteoporosis, and bimonthly cabotegravir and rilpivirine injections for HIV therapy and pre-exposure prophylaxis together mark a step change in the accepted maximum dosing interval for injectable products [26].

Transdermal delivery

Polymeric transdermal patches — matrix (drug-in-adhesive) and reservoir (rate-controlling membrane) designs — sustain systemic delivery of low-dose drugs such as fentanyl, nicotine, clonidine, estradiol and rivastigmine over one to seven days. Polymers such as ethylcellulose, EVA, silicone rubber, polyisobutylene and acrylic pressure-sensitive adhesives provide the structural, permeability and adhesion characteristics required [14].

Ocular delivery

Ocular delivery is severely limited by short pre-corneal residence time; polymeric solutions containing HPMC, PVA or Carbopol extend residence time modestly, while hydrogel-based inserts and polymeric intraocular implants provide more substantially sustained release for months to years. Fluocinolone-acetonide implants for chronic uveitis and dexamethasone implants for macular oedema are established examples of the intraocular polymer implant category [16].

Implantable systems

Long-acting polymeric implants deliver drug at controlled rates over months to years. Contraceptive implants based on levonorgestrel (silicone rubber) and etonogestrel (EVA) provide three- to five-year contraception from a single subdermal device. Buprenorphine implants provide six-month opioid-use-disorder therapy; goserelin, leuprolide and octreotide implants provide long-acting hormonal therapy; and long-acting cabotegravir and rilpivirine formulations, developed during the review period, provide bimonthly HIV therapy or prevention [26].

Pulmonary delivery

Polymeric microparticles for pulmonary delivery — typically large porous PLGA particles with aerodynamic diameters suitable for deep-lung deposition — have been investigated for sustained pulmonary delivery of anti-tubercular, anti-asthmatic and pulmonary hypertension drugs. Adoption in the clinic remains limited, but the platform is a focus of continuing preclinical work [12].

Anticancer delivery

Polymeric anticancer applications include ligand-targeted PLGA nanoparticles for passive and active tumour delivery, injectable in-situ forming implants for local chemotherapy of unresectable tumours, and stimuli-responsive polymeric nanoparticles designed to release payload preferentially in the acidic tumour microenvironment or under intracellular reducing conditions Passively targeted, PEGylated polymeric nanoparticles exploit the enhanced permeability and retention (EPR) effect for preferential tumour accumulation, though the clinical significance of this effect remains a topic of active discussion [20].

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Table 5. Representative therapeutic applications of polymeric controlled- and sustained-release systems by route of administration.

Route	Typical Polymer Systems	Representative Objectives / Products	Ref.
Oral	HPMC/EC matrix; coated pellets; osmotic tablets	Once/twice-daily antihypertensives, antipsychotics, opioids; OROS platform	[8][10][24]
Injectable	PLGA microspheres; in-situ forming implants	Long-acting depots (leuprolide, risperidone, octreotide, LAI cabotegravir)	[11][12][26]
Transdermal	EVA, silicone, acrylic adhesive matrices	1–7 day systemic delivery (fentanyl, estradiol, rivastigmine)	[14]
Ocular	PVA/HPMC gels; PLA/EVA intraocular implants	Prolonged pre-corneal residence; multi-month intraocular implants (dexamethasone, fluocinolone)	[16]
Implantable	Silicone, EVA, PLGA rods & pellets	Contraceptive implants; buprenorphine; long-acting hormonal therapy	[11][26]
Pulmonary	PLGA large porous particles	Sustained pulmonary delivery of anti-TB and anti-asthma drugs (preclinical)	[12]
Anticancer	Polymeric NPs, hydrogels, stimuli-responsive systems	Passive/active tumour targeting; on-demand release	[19][22][23][31]

9. ADVANTAGES, CHALLENGES AND FUTURE PERSPECTIVES

The practical advantages of polymeric controlled- and sustained-release systems are well documented across the reviewed literature. Reduced dosing frequency and smoother plasma concentration profiles improve patient adherence and reduce peak-related toxicity; sustained delivery reduces the total daily fluctuation in plasma drug concentrations, which is particularly valuable for drugs with short half-lives or narrow therapeutic indices; long-acting injectables and implants convert regimens that required daily oral dosing into single-visit therapy over weeks to years, which is particularly transformative in chronic disease management and in populations where adherence is challenging [1][2][11][26].

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The challenges are also well characterised. Dose dumping — sudden release of the entire dose because of formulation failure, physical damage or interaction with alcohol — is a persistent safety concern for high-strength controlled-release products, and has driven substantial regulatory and formulation development effort [1]. Establishing meaningful in vitro–in vivo correlation for complex polymeric systems remains difficult, and biowaiver strategies that work well for immediate-release products often do not extend directly to controlled-release ones. Physical stability, drug–polymer compatibility, moisture sensitivity (particularly for HPMC-based systems), sterility (for injectable and implantable products), and reproducible scale-up from laboratory to commercial batches remain persistent formulation and manufacturing challenges [12][21].

Looking forward, several directions are likely to define the next decade. Stimuli-responsive smart polymers that release drug in response to disease-specific triggers offer the promise of drug release matched in space and time to the biological process being treated [15][19][22][23]. Three-dimensional printing enables personalised dosage forms with complex geometries, patient-specific dosing and combination products that are difficult to achieve by conventional manufacture. Long-acting injectable and implantable products for HIV, contraception, mental health and neurodegenerative disease are expanding rapidly, driven by clear evidence that adherence-driven benefits can substantially improve outcomes [26]. Hybrid polymer–lipid systems, polymer–drug conjugates and polymer nanomedicines with active targeting continue to advance toward the clinic. Together, these developments suggest that polymeric controlled release, already a mature technology, will continue to evolve toward more personalised, more targeted and more clinically transformative therapies.

Table 6. Summary of advantages, challenges and limitations of polymeric controlled-release systems.

Advantages	Challenges / Limitations
Reduced dosing frequency and improved adherence	Risk of dose dumping (mechanical damage, alcohol interaction, formulation failure)
Smoother plasma concentration profiles; reduced peak toxicity	Establishing meaningful in vitro–in vivo correlation (IVIVC) is difficult
Prolonged therapeutic effect (days–years for implants)	Physical/chemical stability of polymer–drug combinations
Design flexibility across matrix, reservoir, osmotic, particulate, hydrogel and implant formats	Scale-up and reproducible manufacture, especially for nano- and microparticles
Options for local, targeted or stimuli-triggered release	Higher unit cost vs immediate-release equivalents
Compatible with biodegradable polymers (no removal needed)	Sterility, endotoxin and residual-solvent control for injectable/implantable products

10. CONCLUSION

Advanced polymeric drug delivery systems have consolidated over the 2011–2022 period as the dominant technological approach to controlled and sustained drug release. Natural, synthetic, biodegradable, non-biodegradable and stimuli-responsive polymers together provide the material palette from which matrix, reservoir, particulate, hydrogel, osmotic, coated multiparticulate and implantable dosage forms are constructed, and mathematical models of diffusion, swelling, degradation and osmotic pumping provide the mechanistic framework for their rational design. Recent pharmaceutical applications span oral, injectable, transdermal, ocular, implantable, pulmonary and anticancer delivery, and include products that have transformed the practical management of hypertension, hormone-responsive cancer, contraception, opioid-use disorder and HIV. Persistent challenges around dose dumping, in vitro–in vivo correlation, stability, sterility and scalable manufacture continue to inform the field, and emerging directions — stimuli-responsive smart polymers, three-dimensional-printed dosage forms, long-acting implants for chronic disease, and polymer-based nanomedicines — suggest that the pace of innovation is if anything accelerating. Polymeric controlled release is likely to remain the technological cornerstone of pharmaceutical product development for the foreseeable future, and its continued advancement will play a central role in delivering safer, more effective and more patient-centred medicines.

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