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Review

Advances in Oral Solid Drug Delivery Systems: Quality by Design Approach in Development of Controlled Release Tablets

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Abstract: Oral solid drug delivery continues to be the gold standard in pharmaceutical formulations, owing to its cost-effectiveness, ease of administration, and high patient compliance. Tablets, the most widely used dosage form, are favored for their precise dosing, simplicity, and economic advantages. Among these, controlled release (CR) tablets stand out for their ability to maintain consistent drug levels, enhance therapeutic efficacy, and reduce dosing frequency, thereby improving patient adherence and treatment outcomes. A well-designed CR system ensures a sustained and targeted drug supply, optimizing therapeutic performance while minimizing side effects. This review delves into the latest advancements in CR formulations, with a particular focus on hydrophilic matrix systems, which regulate drug release through mechanisms such as swelling, diffusion, and erosion. These systems rely on a variety of polymers as drug-retarding agents to achieve tailored release profiles. Recent breakthroughs in crystal engineering and polymer science have further enhanced drug solubility and bioavailability, addressing critical challenges associated with poorly soluble drugs. In terms of manufacturing, direct compression has emerged as the most efficient method for producing CR tablets, streamlining production while ensuring consistent drug release. The integration of the Quality by Design framework has been instrumental in optimizing product performance by systematically linking formulation and process variables to patient-centric quality attributes. The advent of cutting-edge technologies such as artificial intelligence and 3D printing is revolutionizing the field of CR formulations. AI enables predictive modeling and data-driven optimization of drug release profiles, while 3D printing facilitates the development of personalized medicines with highly customizable release kinetics. These innovations are paving the way for more precise and patient-specific therapies. However, challenges such as regulatory hurdles, patent constraints, and the need for robust in vivo validation remain significant barriers to the widespread adoption of these advanced technologies. This succinct review underscores the synergistic integration of traditional and emerging strategies in the development of CR matrix tablets. It highlights the potential of hydrophilic and co-crystal matrix systems, particularly those produced via direct compression, to enhance drug bioavailability, improve patient adherence, and deliver superior therapeutic outcomes. By bridging the gap between established practices and innovative approaches, this field is poised to address unmet clinical needs and advance the future of oral drug delivery.

Keywords: solid dosage forms; oral drug administration; controlled release; quality by design; crystal engineering; dissolution rate; bioavailability

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1. Introduction

Oral drug delivery is the most preferred, traditional, and widely utilized route for administering therapeutic agents. Upon ingestion, the drug dissolves in gastrointestinal fluids and is transported via systemic circulation to its target site. Traditional dosage forms are designed for rapid drug release, leading to fluctuations in drug levels, which may impact therapeutic efficacy and patient compliance [1–3]. Tablets serve as a cornerstone of pharmaceutical formulations, offering precise, convenient, and safe medication delivery. They are available in various types, each tailored to meet specific therapeutic needs based on purpose, release characteristics, and patient requirements [4]. Table 1 provides an overview of tablet types and their key objectives.

Table 1. Types of tablets.

Type	Objective
Conventional Tablets	Immediate drug release
Modified Release (extended release, delayed release, and controlled release) Tablets	Controlled drug delivery
Orally Disintegrating Tablets (ODTs)	Rapid onset of action
Chewable Tablets	Accelerated drug absorption
Effervescent Tablets	
Sublingual and Buccal Tablets	Direct drug absorption into the blood stream (bypass first-pass metabolism)
Coated Tablets	Protection of the active ingredient, taste masking, and controlling the drug release

Managing chronic conditions such as cardiovascular diseases [5], hormone therapy [6], pain management [7], and psychiatric disorders [8] often necessitates frequent dosing of conventional formulations. This can result in poor compliance, inconvenience, and increased risk of side effects. Controlled release dosage forms are designed to maintain steady drug levels, improving patient adherence while reducing side effects and enhancing the safety margin for highly potent drugs [9–11]. Figure 1 [12] illustrates the medical rationale behind controlled drug delivery systems (CDDSs).

Drug release from CR delivery systems is governed by the drug's physicochemical and polymer properties and can be programmed to occur at a predetermined rate over a specific period [13]. Among various CR systems, hydrophilic oral matrices are widely utilized due to their cost-effectiveness and reproducibility of drug release profiles. Monolithic (matrix) systems contain solid drug dispersions [14] within a porous network and are further classified into hydrophilic (water-soluble) and hydrophobic (water-insoluble) matrix systems. Hydrophilic matrix systems are defined as homogenous dispersions of active molecules within a skeleton of hydrophilic polymers [15]. Upon contact with an aqueous medium, hydrophilic polymer chains relax and form a gel layer, regulating drug release. This process is characterized by swelling, polymer dissolution, and/or mass erosion [16–18]. Drug delivery from a hydrophilic matrix system is depicted in Figure 2.

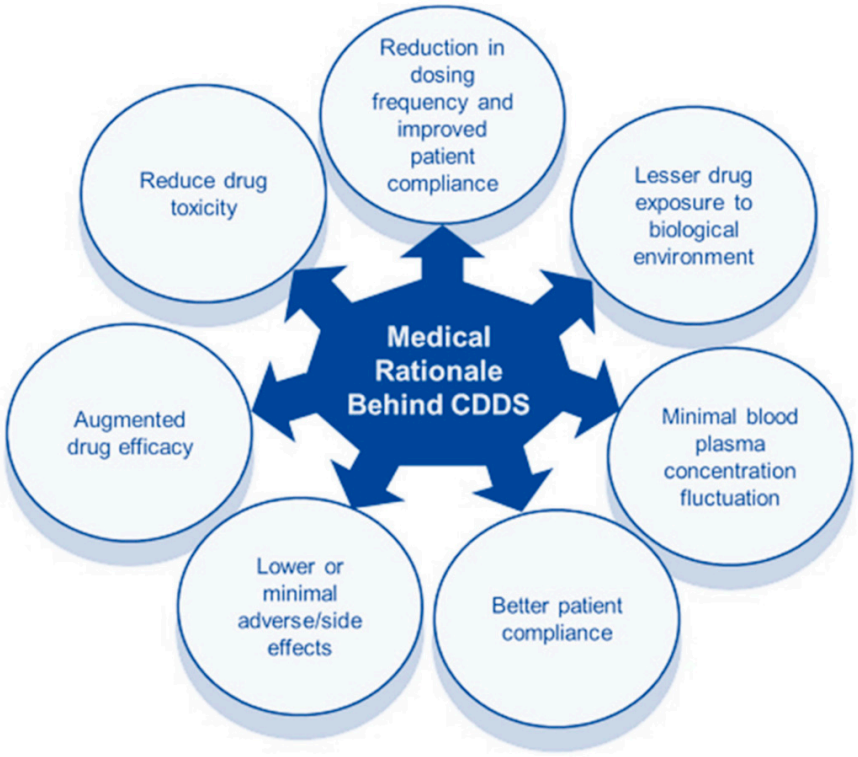


Figure 1. Medical rationale behind controlled drug delivery systems (CDDSs) [12]. Reproduced under the terms of the Creative Commons Attribution License.

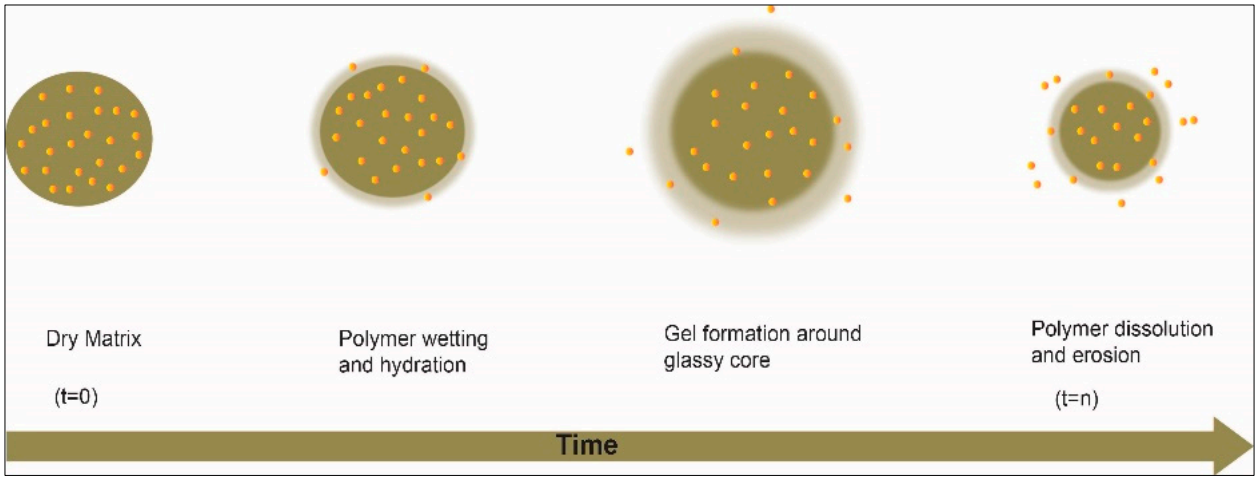


Figure 2. Drug release from a hydrophilic matrix system.

Certain drugs, such as diltiazem hydrochloride, exhibit significant variability in first-pass metabolism, leading to inconsistent bioavailability [19]. Drugs with long half-lives may accumulate, posing a risk of toxicity. Therefore, CR formulations are particularly beneficial for drugs with low oral bioavailability and short elimination half-lives. The selection of appropriate polymers is crucial in CR drug formulations [16]. Moreover, in vitro dissolution testing must reliably predict in vivo behavior, although achieving direct correlations requires comprehensive investigation and validation [20].

Drug release from solid dosage forms is highly dependent on drug dissolution [21]. The Biopharmaceutics Classification System (BCS) categorizes drugs into four classes: Class I (high solubility, high permeability), Class II (low solubility, high permeability), Class III (high solubility, low permeability), and Class IV (low solubility, low permeability).

For Class II and IV drugs, solubility becomes the rate-limiting step in drug release [22]. Additionally, many drugs exhibit pH-dependent solubility, impacting their dissolution and release profile during gastrointestinal transit. Among many other approaches [23,24], enhanced drug solubility can be achieved through crystal engineering techniques, a promising approach in pharmaceutical development. Pharmaceutical cocrystals have revolutionized controlled drug release by allowing active pharmaceutical ingredients (APIs) to be combined with coformers to enhance the solubility, stability, and dissolution rates. These systems are particularly effective for poorly soluble drugs, improving bioavailability and ensuring prolonged drug release with better patient compliance [25]. Cocrystals are solid-state multi-component systems consisting of non-toxic coformers and an active drug ingredient. They allow for the molecular-level engineering of drug formulations. Coformers contain functional groups such as amide, carboxylic acid, alcohol, and amine, enabling the formation of hydrogen bonds with APIs [26–28]. These single-phase crystalline structures often exhibit modified physicochemical properties compared to their individual components. Figure 3 illustrates the crystal engineering approach in developing CR tablets with optimized drug release characteristics.

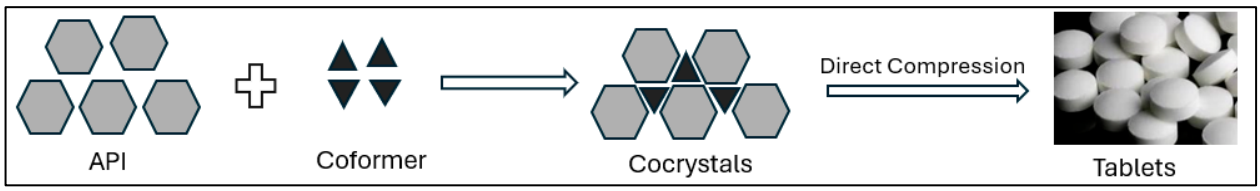


Figure 3. Crystal engineering approach to obtain directly compressed tablets.

Additionally, cocrystals can be engineered to control drug dissolution rates, enabling extended release formulations [29]. The crystal packing structure influences tablet formation, which directly affects the drug release behavior [30]. However, despite their potential, cocrystals require further in vivo validation to replace established methods for poorly soluble drugs [31]. Supersaturating cocrystal systems, when formulated with solubilizing surfactants and precipitation inhibitors, offer a promising solution for improving bioavailability in poorly soluble APIs [32]. This was demonstrated by Childs et al., who used a 1:1 danazol:vanillin cocrystal system to achieve a tenfold increase in bioavailability compared to a conventional suspension [33].

Pharmaceutical QbD (Quality by Design) identifies critical quality attributes and variables and, thereby, modifies both the final product and the product development cycle [34]. QbD elements include the following: identification of Quality Target Product Profile (QTPP) and risk assessment analysis; product and process design and understanding for the identification of CMAs and CPPs; and a control strategy to continuously produce high-quality products [35]. This review underscores the critical importance of Quality by Design (QbD) in the development and refinement of oral controlled release (CR) drug delivery systems. It also explores key mechanisms such as in vitro dissolution modeling and examines how formulation and process variables influence drug release behavior. Additionally, this review highlights the significance of crystal engineering approaches in tailoring drug release profiles and discusses the promising role of pharmaceutical cocrystals in enhancing drug solubility, stability, and extended release performance. Advancements in cocrystal technology, polymer-based CR systems, and dissolution modeling continue to drive innovation in oral drug delivery, offering improved therapeutic efficacy and patient compliance.

2. QbD Guided Development and Product Performance of Controlled Release Matrix Tablets

QbD has evolved with the issuance of ICH Q8 (R2) (Pharmaceutical Development), ICH Q9 (Quality Risk Management), and ICH Q10 (Pharmaceutical Quality System). Pharmaceutical QbD is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and control based on sound science and quality risk management [36]. The QbD strategy identifies quality attributes from the end user's perspective and translates them into critical drug product characteristics. It links formulation and manufacturing variables, including Critical Material Attributes (CMAs), Critical Process Parameters (CPPs), and Critical Quality Attributes (CQAs), to ensure the consistent production of high-quality drug products. While QbD implementation offers several advantages, industries have different levels of understanding, leading to numerous challenges and limitations in QbD methodology adoption. Manufacturing of CR matrix tablets involves complex interactions of several formulation and process variables (Figure 4). The knowledge and interpretation of these complex interactions affecting product quality are imperative [37,38]. Further, the optimization of these variables is crucial to obtain quality products consistently. Risk identification and mitigation is a proactive approach, and the incorrect risk assessment increases the likelihood of unexpected failures producing poor-quality products. An accurate understanding of QbD principles is pivotal in product development to reduce quality issues. A brief description of QbD elements is discussed in the later sections.

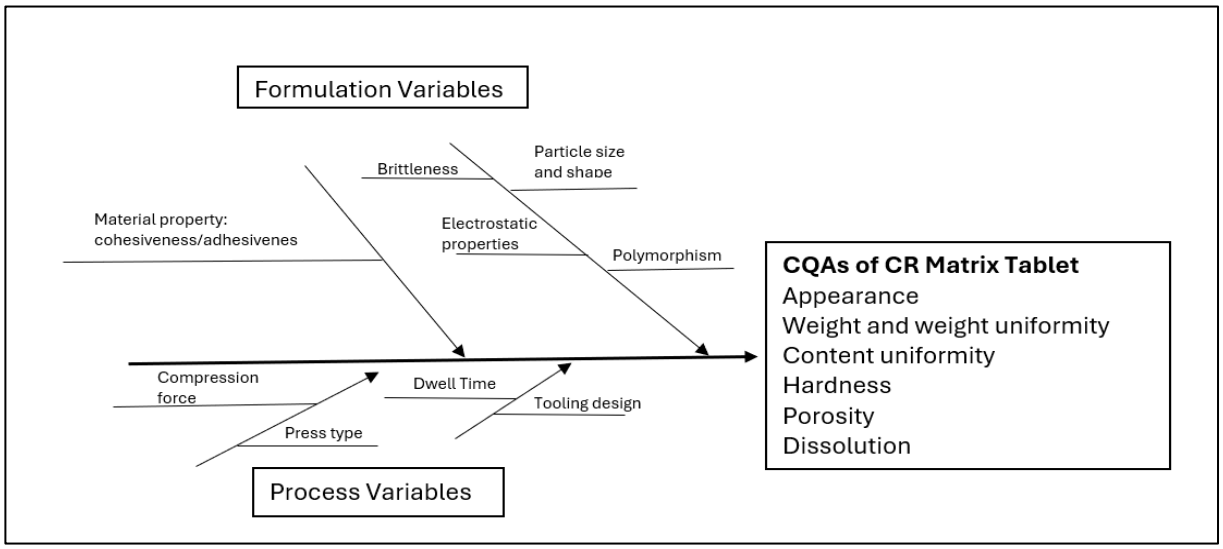


Figure 4. Ishikawa fishbone diagram depicting factors that may significantly impact CQAs.

2.1. Identification of QTPP and Risk Assessment Analysis

QTPP is an anticipated summary of the desired quality attributes of a drug product, aimed at ensuring the intended quality while considering its safety and efficacy [36]. Risk identification followed by a risk analysis are two fundamental units of risk assessment, as mentioned in the International Council for Harmonization (ICH) Q9 document. Both of these units are critical in applying the QbD approach in pharmaceutical product development. Hazard or risk identification deals with information identifying potential risk factors, whereas a risk analysis deals with the severity and occurrence of harm. A risk assessment analysis aims to identify high-risk factors affecting the drug product's CQAs. Figure 4 is an Ishikawa (fishbone) diagram that visually represents the various factors that could affect the critical quality attributes of a product, helping teams to identify and address potential

issues systematically. CQA 'drug dissolution', which influences the release mechanism, is discussed explicitly in the following subsection.

2.2. Tableting: A Key Process Parameter

Tablets are manufactured by dry and wet granulation and direct compression. Direct compression is an affordable tableting technique involving fewer process steps [39] and containing temperature- and moisture-sensitive drugs [40]. Direct compression is defined as an operation by which tablet compacts are obtained by the direct compression of powder blend(s) of active ingredient(s) and excipients [39]. Directly compressed compacts disintegrate into API particles rather than granules upon contact with the dissolution fluid, thereby exhibiting faster dissolution [41]. The subsequent sections elaborate on the diverse facets of directly compressible matrices with an emphasis on hydrophilic and crystal-engineered tablets.

2.3. Controlled Release Matrix Tablets

CR tablet matrices are aimed at providing continuous drug delivery at a preset rate to prolong the blood or tissue therapeutic drug levels. A matrix tablet consists of homogenously dispersed active and inactive ingredients. The mechanism of drug release varies based on the release retardants and is governed by Fick's law of diffusion [10].

2.3.1. Mechanisms of Controlled Release

Controlled release drug delivery systems are designed to release medication at a specific rate, location, and duration to improve the therapeutic outcomes and patient compliance [42]. The key mechanisms are outlined in Table 2. Each mechanism is tailored to the drug's properties and therapeutic needs, enhancing efficacy and minimizing side effects. Drug release mechanisms through swelling-assisted, erosion-controlled, and osmotic drug delivery systems are explained in [43–45], respectively.

Table 2. Mechanisms of controlled drug release.

Controlled Release System		Drug Release Mechanism
Diffusion	Reservoir	The drug is encapsulated in a core surrounded by a permeable membrane. The drug diffuses through the membrane at a controlled rate.
	Matrix	The drug is dispersed in a matrix, and release occurs as the drug diffuses out of the matrix material.
Dissolution		The drug or its coating dissolves gradually, releasing the active ingredient at a controlled rate.
Osmotic		Utilizes osmotic pressure to push the drug out through a small orifice in the dosage form. The release rate is independent of external conditions, like pH.
Erosion		The drug is embedded in a matrix, and release occurs as the matrix erodes over time.
Swelling		The dosage form swells in the presence of bodily fluids, creating pathways for the drug to diffuse out gradually.
Stimuli-Responsive		The drug release is triggered by external stimuli, such as pH, temperature, or enzymes, enabling site-specific drug delivery.

2.3.2. Directly Compressed Tablets Formulated with Hydrophilic Matrix

The drug release in hydrophilic matrices is regulated by swelling, polymer dissolution, and mass erosion. Upon contact with gastrointestinal fluids, the hydrophilic polymers swell, forming a gel layer that controls the release rate. Mathematical models, such as the

Vergnaud equation, are used to predict water uptake and polymer erosion rates. Drugs with high solubility primarily release via diffusion, while poorly soluble drugs rely on matrix erosion.

Swellable polymers and compressed hydrophilic matrices are widely used in oral applications [17,46]. The characteristic feature of these polymers is the glassy-to-rubbery transition that offers controlled drug delivery [17]. This transition occurs due to the lowered transition temperature of the polymer. The individual undisturbed polymeric chains absorb water, leading to an increase in the radius of gyration. This results in an increased matrix volume, and a sharp segregation is observed between the glassy and the rubbery regions [47]. These polymers form versatile hydrophilic macromolecular networks called hydrogels [48]. This hydrated viscous layer acts as a drug release barrier by opposing solvent penetration into the tablet and restricting the solute movement out of the tablet [46]. The solute and solvent movement generates three moving fronts across the matrix: eroding front, diffusing front, and swelling front, governed by the matrix–water boundary, the solid drug–drug solution boundary, and the glassy–rubbery boundary, respectively. The eroding and dissolution fronts move from outside the matrix inward, while the swelling front moves outward until the swelling rate dominates the dissolution rate. The relative movement of the described fronts controls the kinetics of drug release. Over the course of the drug delivery, the swelling and the dissolution fronts synchronize and become identical. This synchronization produces a consistent/zero-order drug release. Synchronization renders the swelling front inactive, and these systems behave as erodible matrices. Constant drug release from such systems is obtained due to synchronization of eroding and diffusing fronts [17]. The contribution of each release mechanism is dependent on the physical and mechanical properties of the viscous gel layer, as well as the drug solubility [49].

While swelling is characterized as a dimensional phenomenon, the rate and degree of hydration can be calculated by the generalized Vergnaud model [50,51] and water uptake capacity [51,52], respectively. The generalized form of the Vergnaud model is mentioned in Equation (1) as follows:

$$M_t = kt^n \quad (1)$$

where M represents the amount of liquid/solvent transferred at time t, and k is the swelling constant that depends on the amount of liquid transferred after infinite time, the porosity of the matrix, and diffusivity. The exponent n indicates the mechanism of water uptake.

Roy and Rohera utilized the Vergnaud model to determine the rate of swelling and the equilibrium weight gain method to determine the water uptake capacity [52]. The percentage of water uptake by tablet matrices can be calculated using Equation (2).

$$\%\ \text{water uptake} = \frac{(W_s - W_i)}{W_P} \times 100 \quad (2)$$

where W_s is the weight of the swollen matrix, W_i is the initial weight of the dry matrix, and W_p is the weight of the polymer in the matrix.

The primary mechanism of release of water-soluble drugs is the diffusion of the dissolved drug molecules through the gel layer, whereas the primary mechanism of poorly water-soluble drugs is by matrix erosion [46]. Numerous authors have described mathematical models to represent the polymer dissolution mechanism of swellable matrix tablets [53,54]. In the initial stages of the in vitro dissolution, two segregated matrix states can be observed: a glassy polymeric state and a rubbery (swollen) state. Progressively, the glassy and the rubbery states synchronize, and true polymer dissolution is observed [53].

The degree of matrix erosion at selected time intervals can be determined by Equation (3) as follows:

$$\% \text{ matrix erosion} = \frac{(W_i - W_t)}{W_i} \times 100 \quad (3)$$

where W_i is the initial dry tablet matrix weight, and W_t is the weight of the tablet matrix subjected to erosion at time t.

2.3.3. Critical Factors Affecting Drug Release

Polymer Characteristics

A decreased rate of drug release was observed with an increased level of hydrophilic polymers. This was noted regardless of the physical and chemical properties of the hydrophilic polymer. An increased amount of the hydrophilic polymer provides a higher degree of physical cross-linking of polymer chains, thereby increasing the tortuous path of the dissolved drug molecules [55]. HPMC (hydroxypropyl methylcellulose) is one of the most widely used hydrophilic polysaccharides. This polymer is non-ionic, water-soluble, and enzyme-resistant and forms a hydrogel when in contact with water [56]. The viscosity of HPMC is a critical factor determining the release mechanism. Factors affecting the polymer viscosity are its molecular weight, chemical structure, and interaction with the solvent. Various authors have studied the impact of polymer viscosity and reported a decline in the drug release rate with the increase in the polymer viscosity [55].

Maggi et al. incorporated two different slightly water-soluble drugs and reported a biphasic release system from double-layer tablets. Out of the two layers, one layer consisted of an HPMC matrix to provide sustained release, while the other was formulated as a fast release. HPMC grades (K4M, K15M, and K100M) and concentrations (10%, 16%, and 22%) were varied to obtain different drug release rates. The results demonstrated that an increase in the content and viscosity grade reduced the drug release rate [57]. Wan et al. studied the effect of water penetration on matrices containing differing concentrations and molecular weights of HPMC. The water uptake by tablet matrices was found to be directly proportional to the concentration and molecular weight of HPMC [58].

Different polymeric mixtures to regulate release profiles are one of the most widely used choices for the formulation of sustained release therapeutic agents [56]. One such widely studied combination is of two cellulose derivatives, ethylcellulose and hydroxypropyl methylcellulose. The polymer mixture of the two prolonged the release of tramadol [59]. In another study, the influence of the HPMC concentration and viscosity grade was studied on the release of diclofenac sodium. The authors reported that an appropriate blend of HPMC and carbopol provided zero-order drug release with reduced fluctuations [60].

Naproxen sodium CR tablets were successfully prepared using QbD principles. A mixture of Eudragit RSPO and RLPO polymers in combination with a disintegrating agent (crosspovidone) was studied to regulate the drug release. A 2^3 study design was used to optimize the tablet formulation. The optimized tablet formulation showed a disintegration time of 88 min and a drug release of up to 14 h in a controlled manner [61].

QbD methodology was used to optimize tofacinitinib citrate CR tablets with HPMC as a release retardant. Formulation variables, such as HPMC, polyethelyene oxide, and magnesium stearate, were optimized simultaneously. Drug dissolution, a critical quality attribute, was assessed using a 2^3 full factorial study design. The authors concluded the optimal formulation ranges for HPMC, polyethelyene oxide, and magnesium stearate to be 14–21 mg, 8–12 mg, and 1–2 mg, respectively, thus producing desired drug dissolution and release [62].

Drug Attributes

Drug solubility and its molecular weight modulate the release through a matrix. Drugs with lower molecular weights can easily diffuse through the gel layer and therefore exhibit lower MDTs (Mean Dissolution Times) than those with higher molecular weights [63]. Ford et al. studied the dissolution of seven different drugs differing in their solubility from hydroxypropyl methylcellulose (HPMC) matrices. The soluble drugs demonstrated a non-Fickian release, while the insoluble drugs showed almost zero-order release [64].

The impact of varying the type of diluent (water-soluble gum arabic and insoluble calcium phosphate) and the diluent/matrix ratio on the drug release behavior from both lipophilic and hydrophilic matrix tablets was examined. Three drugs based on their different water solubility, viz., ketoprofen, theophylline, and sodium sulphadiazine, were selected as the model drugs. The results with the three examined drugs demonstrated the importance of drug solubility on the release rate behavior of drugs from matrix tablet formulations [65].

Another significant attribute affecting the release is drug loading. Incorporating large amounts of drug significantly reduces the polymer content, thereby producing a burst effect [56]. The high amount of drug release has a consequential impact on the release profile. The influence of drug-to-polymer ratio on the release of diclofenac sodium was studied [66].

2.4. Alteration of Drug Properties and Drug Release Modulation via Crystal Engineering

Crystal engineering is a vital strategy in tablet formulation to optimize drug properties such as solubility, stability, and bioavailability. Key techniques include the following:

- Solvent Evaporation and Recrystallization: These traditional methods involve dissolving an API in a suitable solvent and then carefully evaporating the solvent to form a specific crystal structure. By controlling factors like temperature, solvent choice, and concentration, scientists can influence the resulting crystal form [67].
- Milling and Mechanical Activation: High-energy milling can induce polymorphic transformations or the formation of amorphous materials, which often have higher solubility but may require stabilization. Mechanical activation is used to improve the compressibility and flow, which are essential properties for tablet manufacturing [68].
- Spray Drying: This technique allows for the rapid evaporation of a solvent, leading to the formation of microcrystalline or amorphous forms. Spray drying is particularly effective for creating stable dispersions of APIs with improved dissolution rates [69].
- Hot-Melt Extrusion: In this method, an API and excipients are heated and extruded to form a solid dispersion, often in an amorphous state. This technique is suitable for drugs with poor solubility and can be used to improve the tablet performance [70].
- Supercritical Fluid Techniques: Using supercritical CO_2 as a solvent, this technique enables precise control over crystallization conditions, allowing for the formation of unique crystal forms. Supercritical fluid technology is particularly useful for producing small, uniform particles with enhanced dissolution rates [71].

Applications of Crystal Engineering in Matrix Tablet Formulation

- Solubility Enhancement: Many new APIs suffer from poor water solubility, limiting their bioavailability and therapeutic effectiveness. Crystal engineering provides several strategies, such as polymorph selection, co-crystallization, and amorphization, to increase the solubility and dissolution rates [72]. For example, by selecting a more soluble polymorph or forming a co-crystal with a water-soluble coformer, the drug's dissolution rate can be significantly improved, leading to better absorption in the gastrointestinal tract [73].

- Stability Improvement: Chemical and physical stability are crucial for maintaining the efficacy of a drug during its shelf life. Certain polymorphs may be more susceptible to degradation, while others are more stable [74]. Crystal engineering can help identify and select the most stable form of an API, reducing the risk of polymorphic transformations. Co-crystals and salts can also offer enhanced stability under different environmental conditions, protecting the API from degradation due to moisture, temperature, or light [75].
- Optimization of Mechanical Properties: Tablet formulation requires APIs with specific mechanical properties, such as compressibility and hardness. Some crystal forms are more brittle or difficult to compress, posing challenges in the tableting process. By designing crystals with improved mechanical properties, crystal engineering can enhance tablet manufacturability, reducing the likelihood of capping, lamination, or other tableting defects [76].
- Challenges and Limitations: While crystal engineering offers substantial benefits, it also faces challenges. Developing new crystal forms requires extensive screening and characterization, which can be time-consuming and costly [77]. Additionally, the formation of novel polymorphs or co-crystals may raise intellectual property concerns, as existing patents may restrict the use of certain crystal forms [78]. Regulatory challenges are also a significant concern. Regulatory agencies, such as the FDA and EMA, require thorough documentation of the crystal form used in a drug product, and any changes to this form may necessitate re-evaluation. This requirement can make it difficult to implement crystal engineering strategies after a drug has already reached the market [79].

2.5. Compression and Porosity

Compression pressure is an external axial force that is used to press the powder blend inward to form a solid compact. Based on the individual material properties, the powder mixture undergoes a plastic or elastic deformation. Plastic deformation is irreversible, whereas elastic deformation is reversible. The mixture may also undergo fragmentation by breaking the larger particles into smaller discrete ones. Compression pressure may influence dissolution by impacting other tablet properties, such as porosity, hardness, disintegration, etc. [80,81]. The pore structure is generally described by the total porosity, which is a measure of the void space, including open and closed pores within the geometric boundary of the dosage form, matrix tablet [82]. The first stage of drug dissolution is penetration of the solvent into the tablet pores, making tablet porosity a critical parameter [83]. With the increase in the compression force, the tablet porosity is reduced. The force of the compression affects the release rate in a case of low-viscosity polymers. The release rate remains unaffected in high-viscosity polymers [56]. Adeleye et al. studied the effect of compression pressure on the release properties of tramadol and concluded that the drug and excipient material properties had a higher impact compared to the compression pressure [81].

2.6. Kinetic Modeling of Oral Drug Release

Several models can be used for the description of in vitro dissolution [84], and the dissolution data can serve as a surrogate for bioequivalence assessment under specific conditions. These models describe drug dissolution data where the amount of drug dissolved is a function of time (t). The nature of the drug and its polymorphic form, solubility, crystallinity, particle size, and amount in the pharmaceutical dosage form can affect the drug release kinetics. Cumulative drug dissolution profiles are commonly used in opposition to their differential profiles. Dissolution profiles can be described by different

models derived from distinct mathematical functions [21,85]. Figure 5 [86] illustrates the frequency use distribution of the most famous drug release models.

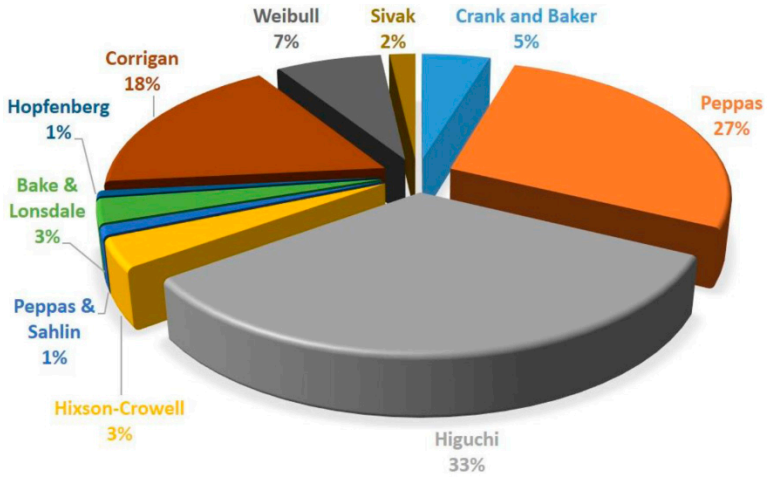


Figure 5. Frequency use distribution of the most famous drug release models [86]. Reproduced under the terms of the Creative Commons Attribution License.

- Zero-Order Model: Drug dissolution from pharmaceutical dosage systems from which the drug is released slowly can be represented by the following equation:

$$f_t = K_0 t \quad (4)$$

where f_t represents the fraction of drug dissolved in time t, and K_0 is a zero-order release constant or a dissolution rate constant [21,85]. This relationship can be used to explain drug dissolution from transdermal systems, matrix tablets, coated forms, osmotic systems, etc. The dosage forms that follow the zero-order model release the same amount of drug per unit time.

- First-Order Model: The application of the first-order model to drug dissolution studies was first proposed by Gibaldi and Feldman [87] and later by Wagner [88]. Absorption and elimination phases have been described by this model. Pharmaceutical dosage forms containing water-soluble drugs in porous matrices follow first-order release kinetics [89]. The drug release is proportional to the amount of drug remaining in the interior of the porous matrix. The first-order model can be described by the following equation:

$$\log Q_t = \log Q_0 + \frac{K_{1t}}{2.303} \quad (5)$$

where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution, and K_1 is the first-order release constant.

- Higuchi Model: Higuchi [90,91] developed theoretical models to study the release of poorly water-soluble and water-soluble drugs from semi-solid or solid matrices. Higuchi describes drug release as a diffusion process based on Fick's law, square-root time dependent. The Higuchi model can be expressed as follows:

$$f_t = K_H t^{1/2} \quad (6)$$

where f_t is the fraction of dissolved drug in time t, and K_H is the Higuchi dissolution rate constant.

- Korsemeyer–Peppas Model: Korsemeyer et al. [92] developed a simple, semi-empirical model, exponentially relating the drug release to the elapsed time (t):

$$M_t/M_\infty = kt^n \quad (7)$$

where M_t/M_∞ is the fraction of drug released at time t, k is the release rate constant, and n is the release exponent. The value of the release exponent n characterizes the drug release mechanism. A value of n = 0.45, 0.45 < n < 0.89, and 0.89 < n < 1 indicates Fickian (Case I), non-Fickian (anomalous), and zero-order (Case II) transport, respectively [52,93].

3. Emerging Approaches for the Customization of Drug Release

3.1. Three-Dimensional (3D) Printing Technology

Three-dimensional printing technology has gained significant attention in the pharmaceutical industry, particularly in the development of controlled release tablet formulations. This technology allows for the precise design of dosage forms with tailored release profiles, which can offer several advantages over conventional methods [94]. Figure 6 [95] exemplifies applications of 3D printing in personalized medicine.

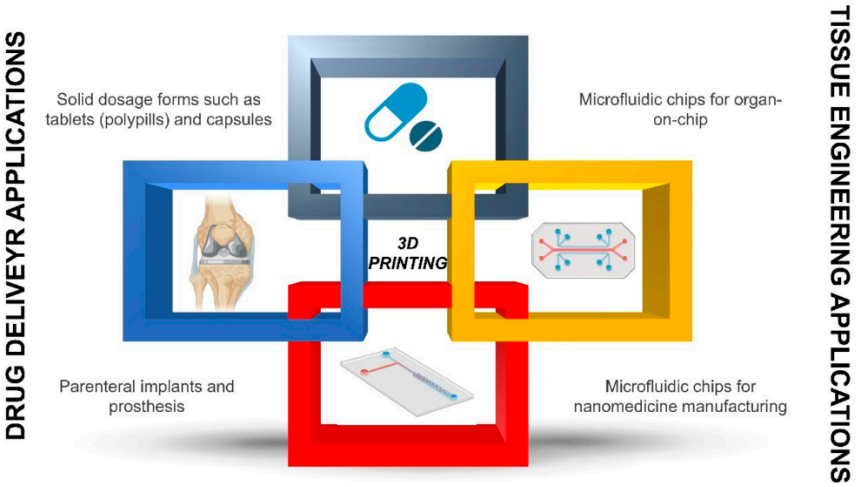


Figure 6. Application of 3D printing in personalized medicine [95]. Reproduced under the terms of the Creative Commons Attribution License.

3.1.1. Layer-by-Layer Printing

3D printing allows for the fabrication of tablets with specific patterns or structures, which can control the release rate of the drug. By manipulating the porosity, size, and shape of the layers, the release of active pharmaceutical ingredients (APIs) can be optimized to achieve sustained or delayed drug delivery [96].

3.1.2. Multi-Drug Delivery

3D printing can facilitate the incorporation of multiple drugs within a single tablet, each with a distinct release rate. This can be beneficial for combination therapies or for managing multiple conditions simultaneously [97].

3.1.3. Types of 3D Printing Techniques Used in Pharmaceutical Applications

Different types of 3D printing techniques [98–101] to control the drug dosing and obtain tailored release profiles are described in Table 3.

Table 3. 3D printing techniques.

3D Printing Technique	Description
Fused Deposition Modeling (FDM)	Heating and extruding material to build the tablet layer by layer.
Stereolithography (SLA)	Usage of UV light to cure liquid resin layer by layer to create solid objects. This method allows for the fabrication of highly detailed structures.
Selective Laser Sintering (SLS)	Usage of a laser to sinter powdered materials, creating a solid object.
Inkjet Printing	Deposition of liquid droplets onto a substrate to build the tablet. It can be used to directly print APIs or excipients.

The impact of 3D printing (3DP) coatings on drug release mechanisms and rates was investigated as a potential strategy to prevent alcohol-induced dose dumping. Three types of matrix tablets—hydrophilic, lipophilic, and a combination of both—were formulated using direct compression and then coated via 3DP. Coating materials included a commercial polyvinyl alcohol (PVA) filament and a hypromellose-based filament produced through hot-melt extrusion (HME). These materials were analyzed at different stages of the coating process using SEM, DSC, Raman spectroscopy, and PXRD. The dissolution profiles of both uncoated and 3DP-coated tablets were evaluated in strongly acidic (pH 1.2) and alcoholic (40% ethanol) media. Dissolution testing in alcoholic media demonstrated that the Affinisol coating effectively prevented dose dumping. Additionally, testing in acidic conditions indicated that the Affinisol coating could also serve to delay the release of active pharmaceutical ingredients [102].

Fused Deposition Modeling (FDM) was utilized to design and fabricate a bilayer tablet containing isoniazid (INZ) and rifampicin (RFC) for tuberculosis treatment. INZ was incorporated into a hydroxypropyl cellulose (HPC) matrix to enable the release in the stomach under acidic conditions, while RFC was embedded in a hypromellose acetate succinate (HPMC-AS) matrix to ensure release in the upper intestine under alkaline conditions. This formulation strategy aims to enhance clinical efficacy by reducing RFC degradation in acidic environments and potentially minimizing drug–drug interactions. The bilayer tablet was produced by first preparing drug-loaded filaments via hot-melt extrusion (HME), followed by 3D printing. Both the HME and FDM processes were optimized to prevent drug degradation and ensure uniform deposition of drug-containing layers. The in vitro drug release was fine-tuned by adjusting the drug loading, infill density, and the number of covering layers. The results showed that over 80% of INZ was released within 45 min at pH 1.2, while approximately 76% of RFC was released within 45 min after transitioning to a pH 7.4 medium. This study demonstrates the promising application of FDM technology for developing personalized oral fixed-dose combination therapies [103].

3D printing technology offers a promising approach for developing controlled release tablet formulations with customized drug release profiles, enhanced bioavailability, and the potential for personalized medicine. However, challenges in material selection, regulatory approval, and scalability remain, which need to be addressed for broader adoption in the pharmaceutical industry [104].

3.2. Use of Artificial Intelligence in Controlled Release Formulation Development

Artificial intelligence (AI) is transforming pharmaceutical formulation development, particularly in the area of controlled release drug delivery systems. AI can optimize and accelerate the design, testing, and manufacturing processes of controlled release formulations, offering several benefits, including improved efficiency, accuracy, and the potential for personalized medicine [105]. Figure 7 is a schematic representation of the main stages during the drug discovery and drug development process. The star represents the stages where AI plays a key role in the pharmaceutical processes [106].

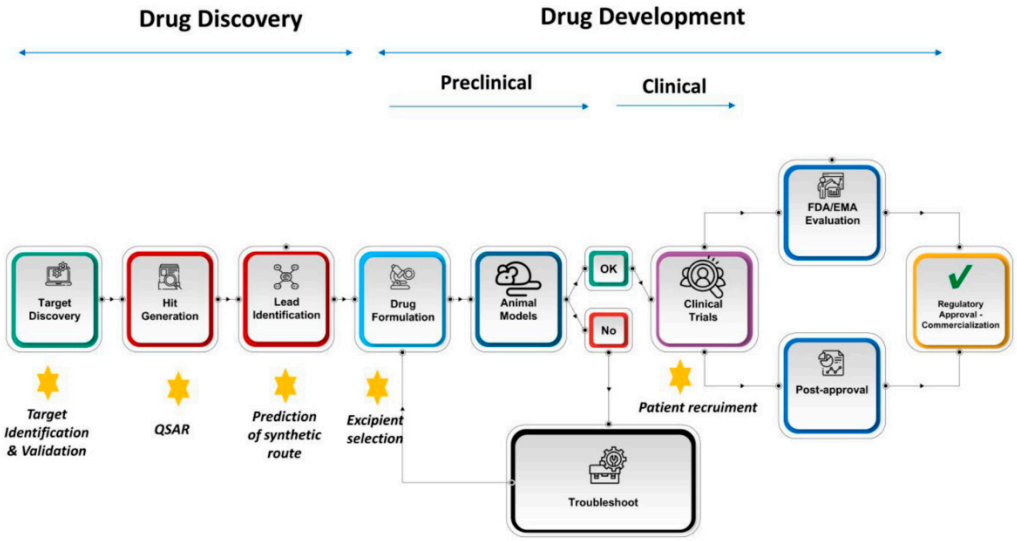


Figure 7. Schematic representation of the main stages during the drug discovery and drug development process [106]. The star represents the stages where AI plays a key role in the pharmaceutical processes. Reproduced under the terms of the Creative Commons Attribution License.

- Predicting Drug Release Profiles: AI algorithms, particularly machine learning (ML) and deep learning, can be trained to predict the release profiles of drugs based on a set of input variables, such as the physicochemical properties of the drug, excipients, and formulation methods. These models can optimize the release rates and duration, ensuring that the formulation meets the therapeutic goals [107].
- Data-Driven Formulation Strategies: AI can analyze large datasets from various stages of formulation development, including experimental results, clinical trials, and real-time manufacturing data. By recognizing patterns in these data, AI can provide insights into the most effective formulation strategies, including optimal excipients for controlled release systems based on their properties, such as solubility, permeability, and biodegradability. AI models can also optimize the concentration and combinations of excipients to control drug release over time [108].
- Process Optimization: Machine learning models can be used to optimize the manufacturing processes, including hot-melt extrusion, granulation, and spray drying, which are commonly used in controlled release formulations. AI can identify the optimal parameters (e.g., temperature, pressure, and speed) to improve the efficiency, reduce batch variability, and ensure consistent drug release [109].
- Simulation of Release Mechanisms: AI-powered in silico models simulate the drug release process within different environments, such as varying pH levels in the gastrointestinal tract. This can help predict how the drug will behave in vivo, allowing for a better formulation design without the need for extensive in vivo testing [106].
- Stability Studies: AI can assist in predicting the stability of controlled release formulations over time under various storage conditions (e.g., temperature, humidity). This helps to design more stable formulations, ensuring the drug's efficacy is maintained throughout its shelf life [110].
- Improving Bioavailability: AI models can optimize controlled release formulations to improve the bioavailability of poorly soluble drugs. By predicting the optimal particle size, excipient composition, and release kinetics, AI can enhance drug absorption and therapeutic outcomes [111].
- Virtual Screening and Testing: Before physical testing of the formulations, AI can be used to perform virtual screening of the excipients, drug compounds, and formulation

strategies. This reduces the time and cost of physical experimentation and helps identify the most promising candidates for further development [111,112].

- Animal Testing Alternatives: AI models can simulate the pharmacokinetics (PK) and pharmacodynamics (PD) of controlled release formulations, reducing the need for extensive animal testing. This aligns with the growing trend toward reducing animal use in research and development [113].

The integration of AI into controlled release formulation development offers transformative opportunities in the pharmaceutical industry. From optimizing formulation designs and manufacturing processes to enabling personalized medicine and enhancing drug stability, AI holds the potential to revolutionize drug delivery systems. While challenges remain, particularly in terms of regulatory acceptance and the integration of AI with traditional pharmaceutical workflows, the future of AI in controlled release formulation development is promising, with the potential to improve patient outcomes and reduce costs [114–116].

A series of two case studies validated the use of generative AI for a pharmaceutical formulation development approach. The authors introduced an innovative generative AI approach that synthesizes realistic digital representations of pharmaceutical products from images of existing formulations. They used the structural features from X-ray microscopy (XRM) and focused on ion beam scanning electron microscopy (FIB-SEM) images of exemplar formulations. These digital structures are optimized using attributes such as particle size and drug distribution, enabling in silico experimentation. The first study involved determining the percolation threshold for microcrystalline cellulose (MCC) in oral solid dosage forms, achieving a precise threshold of 4.2% weight. The second one applied the method to engineer particle distribution in a long-acting HIV inhibitor implant. The generative AI demonstrated the capability to predict structural and performance characteristics accurately, comparable to physical samples. However, the study emphasizes the need for further validation, particularly in regulatory contexts, and highlights limitations related to training data and imaging methods [117].

Artificial neural network (ANN) techniques are commonly employed in pharmaceutical research to screen data and predict experimental outcomes. A study applied Artificial Neural Networks (ANN) and Response Surface Methodology (RSM) as dual optimization tools to develop controlled-release rivaroxaban (RVX) osmotic tablets. Key formulation variables—polyethylene oxide types, osmotic agents, membrane thickness, and orifice size—were optimized using Central Composite Design (CCD). An ANN model predicted optimal formulations, which were validated using in vitro tests and CCD profiling. PBPK modeling via GastroPlus™ simulated in vivo profiles under fasting and fed states, showing zero-order RVX release for 12 h. Predicted and optimized formulations showed no significant differences (ANOVA) and had shelf lives of 22.47 and 17.87 months. PBPK results indicated enhanced RVX bioavailability in the fasted (up to 80%) and fed state (up to 98.5%) from the osmotic tablets versus immediate-release forms. The study confirms ANN's utility in modeling complex osmotic systems [118].

4. Conclusions and Future Perspectives

Drug release is dependent on drug dissolution, and BCS Class II and IV drugs exhibit poor solubility and, therefore, a diminished dissolution rate when embedded in polymer matrices. Solid dispersion techniques can improve the dissolution of poorly water-soluble drugs. Lipid-based CR matrix delivery systems typically consist of waxes, fatty acids, glycerides, etc., as the primary matrix formers and are a remarkable choice for the delivery of poorly water-soluble drugs. Drug solubility can be further augmented by the integration of nanoparticles into CR matrix tablets.

Although controlled release tablets provide substantial advantages, a major drawback is the limited loading capacity for bulky and heavy-dose drugs. Drug micronization, polymer–drug interaction studies, and usage of high compressibility fillers can aid the drug loading capacity. Another significant limitation of CR tablets is the undesirable therapeutic outcome. This can be overcome by the usage of smart polymers that respond to specific triggers, such as temperature, pH, etc. This allows for the development of sophisticated controlled release delivery systems to improve the patient response. Three-dimensional printing technology offers exciting possibilities for customized tablet formulations with specific release profiles. By integrating crystal engineering principles with 3D printing, it may be possible to design tablets that offer personalized medicine, delivering the right dose and release profile tailored to each patient's needs.

The implementation of the QbD approach has reduced the experimental workload for the optimization of CR pharmaceutical formulations. By integrating systematic risk assessments, design of experiments (DoEs), and critical quality attribute (CQA) identification, QbD enables a deeper understanding of formulation and process variables, leading to more robust and predictable drug products. As the pharmaceutical industry continues to shift toward data-driven and patient-centric approaches, QbD serves as a foundational framework for achieving consistent product quality and performance. Looking ahead, emerging trends in QbD-based strategies—such as the incorporation of machine learning, real-time process analytical technologies (PATs), and model-informed drug development (MIDD)—are expected to further streamline the formulation design and accelerate the regulatory approval. These advancements will not only enhance the therapeutic outcomes but also align with the evolving regulatory expectations for innovative and adaptive drug delivery solutions.

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