INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

Co-Processed Excipients in Sustained Release Tablet: A Quality by Design-Based Review

Darshana Deshmukh*, Milke R.

Department of Pharmaceutics, Durgamata Institute of Pharmacy, Dharmapuri, Parbhani, Maharashtra 431401.

ARTICLE INFO

Published: 05 May 2026
Keywords:
Co-Processed Excipients, Sustained Release Tablet, Design-Based Review
DOI:
10.5281/zenodo.20038628

ABSTRACT

Sustained release (SR) tablets are designed to release therapeutic agents at a predetermined rate, improving patient compliance, reducing dosing frequency, and maintaining consistent plasma drug levels. Traditional excipients often face limitations such as poor compressibility, flow, and stability, which can compromise the performance of SR formulations. Co-processed excipients, developed by combining two or more excipients through specialized processing techniques such as spray drying, melt granulation, co-precipitation, and solvent evaporation, offer enhanced mechanical, flow, and functional properties. Integrating the Quality by Design (QbD) approach in the development of SR tablets enables a systematic, science- and risk-based framework that ensures product quality is built into the formulation. Core elements of QbD, including Quality Target Product Profile (QTPP), Critical Quality Attributes (CQA), Critical Material Attributes (CMA), and Critical Process Parameters (CPP), coupled with tools such as risk assessment, Design of Experiments (DoE), and statistical modeling, allow precise optimization of co-processed excipient-based formulations. The application of QbD facilitates reduced batch failures, improved regulatory flexibility, and development of robust and reproducible tablets. Future trends such as artificial intelligence-driven formulation optimization, advanced co-processing techniques, and continuous manufacturing are expected to further enhance SR tablet development. Overall, the combination of co-processed excipients and QbD represents a strategic pathway for producing high-quality, patient-centric sustained release formulations.

INTRODUCTION

Oral drug delivery remains the most preferred route of administration due to its convenience, patient acceptability, and cost-effectiveness. Among various oral dosage forms, tablets dominate the pharmaceutical market owing to their ease of manufacturing, stability, and accurate

***Corresponding Author:** Darshana Deshmukh
Address: *Department of Pharmaceutics, Durgamata Institute of Pharmacy, Dharmapuri, Parbhani, Maharashtra 431401*
Email ✉: ameenpathodi@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

dosing. However, conventional immediate-release formulations often result in fluctuating plasma drug concentrations, leading to suboptimal therapeutic outcomes and potential side effects. To overcome these limitations, sustained release (SR) drug delivery systems have been extensively developed [7].

Sustained release tablets are designed to release the active pharmaceutical ingredient (API) at a predetermined rate in order to maintain a constant drug concentration in systemic circulation for an extended period. Unlike conventional dosage forms, SR systems aim to reduce the frequency of dosing while ensuring prolonged therapeutic efficacy. The mechanism of drug release from SR formulations typically involves diffusion, erosion, swelling, or a combination of these processes [9]. Hydrophilic matrix systems, particularly those based on polymers such as hydroxypropyl methylcellulose (HPMC), are widely used due to their ability to form a gel barrier that controls drug release [4].

The primary advantage of sustained release tablets lies in their ability to maintain steady plasma drug levels, thereby minimizing peak-trough fluctuations. This contributes to improved therapeutic efficacy and reduced toxicity. Additionally, SR formulations enhance patient compliance by reducing dosing frequency, which is particularly beneficial in chronic conditions such as hypertension, diabetes, and cardiovascular diseases [7]. Improved compliance often translates into better clinical outcomes and reduced healthcare costs. Furthermore, SR systems can reduce local irritation in the gastrointestinal tract by avoiding high drug concentrations at specific sites.

Despite these advantages, the development of sustained release formulations presents several challenges, particularly with respect to excipient selection and formulation design. Conventional excipients, which are typically used individually, often fail to provide the desired multifunctional properties required for SR systems. For instance, a single excipient may exhibit good flow properties but poor compressibility, or vice versa [10]. This limitation necessitates the use of multiple excipients, which can lead to formulation complexity, increased production costs, and potential incompatibilities. Moreover, issues such as poor content uniformity, segregation during processing, and variability in drug release profiles can arise when using conventional excipients [3].

To address these challenges, the concept of co-processed excipients has emerged as a promising approach in pharmaceutical formulation development. Co-processed excipients are combinations of two or more excipients that are physically modified through processes such as spray drying, melt granulation, or solvent evaporation to achieve superior functionality compared to simple physical mixtures [8]. Importantly, co-processing does not involve chemical modification, thereby preserving the regulatory acceptance and safety profiles of the individual components. The resulting excipients exhibit improved physicochemical and mechanical properties, including enhanced flowability, compressibility, dilution potential, and stability [3].

In the context of sustained release tablet formulation, co-processed excipients offer significant advantages. They can be engineered to provide controlled drug release while simultaneously improving manufacturability. For example, combining a hydrophilic polymer with a filler can result in a matrix system that exhibits both controlled swelling behavior and good compressibility. Additionally, co-processed excipients can reduce batch-to-batch variability and improve the robustness of the formulation, which is essential for large-scale production [4].

However, the successful development of formulations using co-processed excipients

requires a systematic and scientific approach. Traditional formulation development methods often rely on trial-and-error experimentation, which can be time-consuming, resource-intensive, and inefficient. Such approaches do not provide a thorough understanding of the relationship between formulation variables and product performance.

This need has led to the adoption of the Quality by Design (QbD) approach in pharmaceutical development. Quality by Design is a systematic framework that emphasizes building quality into the product from the initial stages of development rather than relying solely on end-product testing [1]. It involves a thorough understanding of formulation and process variables and their impact on critical quality attributes (CQAs) of the final product. By identifying and controlling critical material attributes (CMAs) and critical process parameters (CPPs), QbD ensures consistent product quality and performance [2].

In the development of sustained release tablets using co-processed excipients, the application of QbD provides several advantages. It facilitates the identification of key factors influencing drug release, such as polymer concentration, excipient ratio, and compression force. Through the use of statistical tools such as Design of Experiments (DoE), it is possible to systematically evaluate the effects of multiple variables and their interactions [5]. This not only accelerates the development process but also enhances the robustness and reliability of the formulation.

Furthermore, QbD aligns with regulatory expectations set by international agencies, as it promotes a science-based and risk-oriented approach to pharmaceutical development. Regulatory guidelines encourage the implementation of QbD principles to achieve better product understanding and lifecycle management [6]. In this context, the integration of co-processed excipients with QbD principles represents a modern and efficient strategy for the development of sustained release tablets.

In conclusion, sustained release tablets play a crucial role in improving therapeutic outcomes and patient compliance. While conventional excipients present certain limitations, co-processed excipients offer a viable solution by enhancing functionality and performance. The application of Quality by Design further strengthens the formulation process by providing a systematic and scientific framework for optimization. Together, these approaches contribute to the development of robust, efficient, and high-quality sustained release drug delivery systems.[8]

3. Sustained Release Drug Delivery Systems

Sustained release (SR) drug delivery systems are designed to deliver a drug at a predetermined rate over an extended period, thereby maintaining a consistent therapeutic concentration in the bloodstream. These systems are particularly beneficial for drugs with short biological half-lives, narrow therapeutic indices, or those requiring long-term therapy. [9] By controlling the rate and duration of drug release, SR formulations minimize fluctuations in plasma drug levels, reduce dosing frequency, and improve patient compliance. Among various SR approaches, matrix tablets are the most widely used due to their simplicity, cost-effectiveness, and ease of manufacturing. [10]

Mechanisms of Drug Release

The release of drugs from sustained release systems is governed by several mechanisms, primarily diffusion, erosion, and osmotic pressure. These mechanisms may act independently or in combination, depending on the formulation design and excipients used. [11]

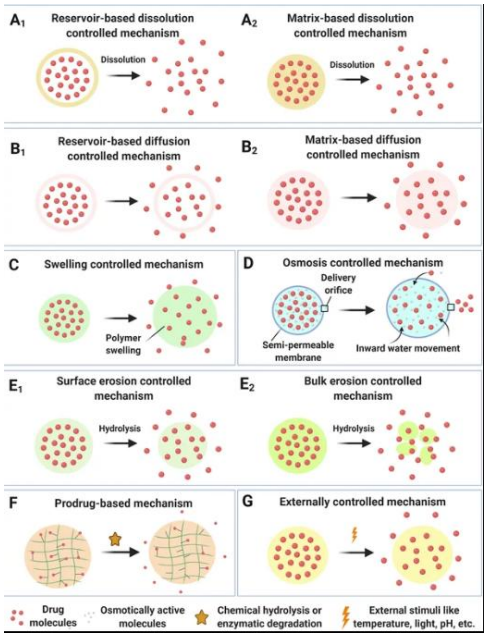

Figure 1: Schematic representation of major drug release mechanisms including diffusion, erosion, swelling, and osmotic systems.

1. Diffusion Mechanism: Diffusion is one of the most common mechanisms in SR formulations, especially in matrix systems. In this process, the drug diffuses from the dosage form into the surrounding dissolution medium through a polymeric barrier. When hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) come into contact with gastrointestinal fluids, they hydrate and swell to form a gel layer around the tablet. This gel layer acts as a diffusion barrier, controlling the rate at which the drug is released. The rate of diffusion depends on factors such as the thickness of the gel layer, drug solubility, and polymer viscosity. [12]

2. Erosion Mechanism: In erosion-controlled systems, drug release occurs as a result of the gradual degradation or dissolution of the polymer matrix. This is typically observed in formulations containing biodegradable or water-soluble polymers. As the outer layers of the tablet erode, the embedded drug is released into the surrounding medium. Erosion can be either surface erosion or bulk erosion, depending on the nature of the polymer. Hydrophilic polymers like HPMC often exhibit a combination of swelling, diffusion, and erosion mechanisms. [12-14]

3. Osmotic Systems: Osmotic-controlled drug delivery systems utilize osmotic pressure as the driving force for drug release. These systems typically consist of a core containing the drug and osmotic agents, surrounded by a semi-permeable membrane. When the tablet comes into contact with gastrointestinal fluids, water permeates through the membrane into the core, creating osmotic pressure. This pressure pushes the drug solution or suspension out through a small orifice at a controlled rate. Osmotic systems are highly reliable and provide zero-order drug release, which is independent of pH and gastrointestinal motility. [15]

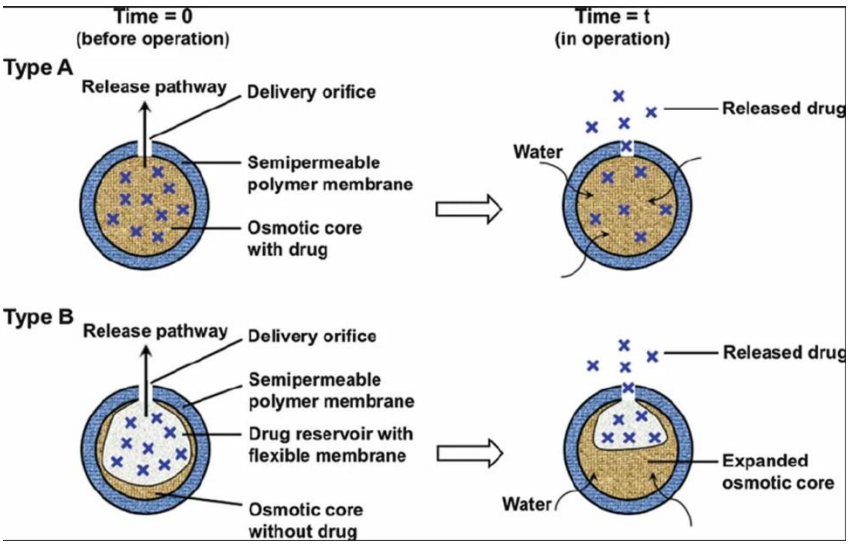

Figure 3: Osmotic-controlled drug delivery system

Polymers Used in Sustained Release Formulations

Polymers play a critical role in controlling drug release from SR formulations. They act as matrix formers, release retardants, and gel-forming agents. Based on their origin and properties, polymers used in SR systems can be broadly classified into hydrophilic and hydrophobic types.

Hydrophilic Polymers: Hydrophilic polymers are widely used due to their safety, availability, and ease of formulation. Hydroxypropyl methylcellulose (HPMC) is the most commonly used polymer in SR matrix tablets. Upon hydration, HPMC forms a viscous gel layer that controls drug diffusion and erosion. Other hydrophilic polymers include hydroxypropyl cellulose (HPC), polyethylene oxide (PEO), and sodium carboxymethyl cellulose (NaCMC). These polymers are particularly suitable for drugs with moderate to high solubility. [16,17]

Hydrophobic Polymers: Hydrophobic polymers such as ethyl cellulose, cellulose acetate, and polymethacrylates are used to retard drug release by forming an insoluble matrix. These polymers do not swell significantly in aqueous media, and drug release primarily occurs through diffusion via pores and channels within the matrix. Hydrophobic polymers are often used for poorly water-soluble drugs to achieve controlled release. [18]

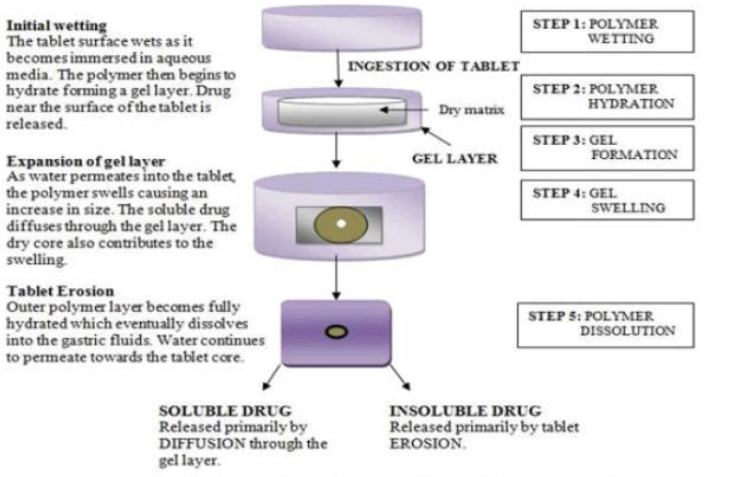

Figure 2: Mechanism of drug release from hydrophilic matrix tablets

Natural and Semi-Synthetic Polymers: In addition to synthetic polymers, natural polymers like xanthan gum, guar gum, and alginates are also used in SR formulations due to their biocompatibility and biodegradability. Semi-synthetic polymers, derived from natural sources, offer improved functionality and consistency. [19]

Factors Affecting Drug Release [20]

The performance of sustained release tablets is influenced by several formulation and process variables. Understanding these factors is essential for designing robust and effective SR systems.

1. Drug Solubility: Drug solubility plays a crucial role in determining the release rate. Highly water-soluble drugs tend to dissolve rapidly, which may lead to dose dumping if not properly controlled. In such cases, higher polymer concentrations or hydrophobic polymers are used to slow down drug release. Conversely, poorly soluble drugs may exhibit slow and incomplete release, requiring the use of solubilizing agents or hydrophilic polymers to enhance dissolution.

2. Matrix Composition: The type and concentration of polymers used in the matrix significantly influence drug release behavior. Increasing the polymer concentration generally results in a thicker gel layer, which slows down drug diffusion. The ratio of hydrophilic to hydrophobic polymers can be optimized to achieve the desired release profile. Additionally, the presence of fillers, binders, and co-processed excipients can affect matrix integrity and drug release kinetics.

3. Tablet Hardness: Tablet hardness, which is influenced by compression force during manufacturing, affects the porosity and density of the matrix. Harder tablets have lower porosity, which reduces the penetration of dissolution medium and slows down drug release. On the other hand, softer tablets may disintegrate more easily, leading to faster drug release. Therefore, optimizing compression force is critical to achieving consistent and controlled release profiles.

4. Co-Processed Excipients

Co-processed excipients represent an advanced approach in pharmaceutical formulation development, particularly for solid oral dosage forms. They are defined as combinations of two or more excipients that are physically modified through specialized processing techniques to enhance their functional performance without undergoing any significant chemical change [21]. Unlike simple physical mixtures, co-processed excipients are engineered at the sub-particle level, resulting in synergistic improvements in physicochemical and mechanical properties. This concept has gained considerable attention in recent years due to its ability to address the limitations associated with conventional excipients.

One of the major advantages of co-processed excipients is their improved compressibility, which is essential for the production of robust tablets, especially in direct compression processes. By combining excipients with complementary properties, such as a brittle material with a plastic one, co-processed systems exhibit superior compactibility and mechanical strength compared to individual components [22]. This results in tablets with adequate hardness and reduced friability.

Another important benefit is the enhancement of flow properties. Poor flowability is a common issue with many pharmaceutical powders, leading to challenges in uniform die filling and content uniformity. Co-processing techniques modify particle size, shape, and surface characteristics, thereby improving powder flow and ensuring consistent tablet weight and drug distribution [23].

Reduced segregation is another significant advantage. In conventional formulations, differences in particle size and density among excipients can lead to demixing during handling

and processing. Co-processed excipients, however, form integrated particles that minimize the risk of segregation, ensuring better uniformity in the final product [21]. Additionally, these excipients contribute to enhanced stability, both physically and chemically, by improving compatibility between formulation components and reducing moisture sensitivity [24].

Various methods are employed for the preparation of co-processed excipients, each offering distinct advantages depending on the desired functionality. **Spray drying** is one of the most widely used techniques. In this method, a solution or suspension containing the excipients is atomized into a hot drying chamber, resulting in the rapid formation of uniform, spherical particles. Spray-dried excipients typically exhibit excellent flowability and compressibility, making them highly suitable for direct compression applications [22].

Melt granulation involves the use of a meltable binder that softens or melts during processing, binding the excipient particles together. This technique eliminates the need for solvents and produces granules with improved mechanical strength and controlled release properties. It is particularly useful for moisture-sensitive drugs and excipients [23].

Co-precipitation is another method in which excipients are dissolved in a common solvent and then precipitated together by altering the solvent conditions, such as pH or temperature. This process results in the formation of intimately mixed particles with uniform composition and enhanced functional properties [24].

Solvent evaporation is a technique where excipients are dissolved or dispersed in a volatile solvent, followed by evaporation of the solvent to yield a solid composite. This method allows for the formation of homogeneous mixtures with improved particle characteristics and is often used for preparing modified-release systems [22].

5. Quality by Design (QbD) Approach

Quality by Design (QbD) is a modern, science- and risk-based approach to pharmaceutical development that emphasizes building quality into a product from the initial stages rather than relying solely on end-product testing. The concept was introduced through regulatory guidelines such as ICH Q8 (R2) and has become a fundamental framework for ensuring consistent product performance and regulatory compliance [26]. QbD focuses on understanding the relationship between formulation variables, process parameters, and product quality attributes, thereby enabling the development of robust and reproducible pharmaceutical products.

- **Concept of QbD**

The central principle of QbD is that quality should be designed and built into the product, not merely tested at the end. This approach involves a thorough understanding of materials, processes, and their interactions. By applying scientific knowledge and risk management principles, QbD ensures that the final product consistently meets predefined quality criteria. It also facilitates continuous improvement and lifecycle management, allowing for flexibility in manufacturing without compromising product quality [27]. In the context of sustained release formulations, QbD helps in achieving desired drug release profiles while maintaining consistency across batches.

- **Key Components of QbD**

1. Quality Target Product Profile (QTPP): QTPP is a prospective summary of the desired quality characteristics of a finished pharmaceutical product. It includes parameters such as dosage form, route of administration, strength, drug release profile, stability, and pharmacokinetic properties. QTPP serves as a foundation for formulation development and guides the identification of critical quality attributes [26].

2. Critical Quality Attributes (CQA): CQAs are the physical, chemical, biological, or microbiological properties that must be controlled within predefined limits to ensure product quality. For sustained release tablets, CQAs typically include drug release rate, tablet hardness, friability, content uniformity, and stability. Identifying CQAs is crucial because they directly impact the safety and efficacy of the product [28].

3. Critical Material Attributes (CMA): CMAs refer to the properties of raw materials (API and excipients) that can influence the CQAs. Examples include particle size, polymorphic form, moisture content, and viscosity of polymers. In SR formulations, the characteristics of polymers such as hydroxypropyl methylcellulose (HPMC) significantly affect drug release behavior. Proper control and selection of CMAs are essential for achieving consistent product performance [29].

4. Critical Process Parameters (CPP): CPPs are the key variables in the manufacturing process that can affect CQAs if not properly controlled. These include parameters such as mixing time, granulation conditions, drying temperature, and compression force. For example, compression force directly influences tablet hardness and porosity, which in turn affect drug release. Identifying and controlling CPPs ensures reproducibility and robustness of the manufacturing process [28].

- **Tools Used in QbD**

1. Risk Assessment: Risk assessment is a systematic process used to identify, analyze, and prioritize factors that may affect product quality. Tools such as Failure Mode and Effects Analysis (FMEA) and Ishikawa (fishbone) diagrams are commonly used. FMEA evaluates potential failure modes and their impact, helping to prioritize critical variables, while Ishikawa diagrams visually represent the relationship between causes and effects. These tools enable formulators to focus on high-risk factors during development [27].

2. Design of Experiments (DoE): DoE is a statistical tool used to systematically study the relationship between multiple input variables and output responses. It allows simultaneous evaluation of several factors and their interactions, reducing the number of experiments required compared to traditional methods. Common designs include factorial design, Box–Behnken design, and central composite design. In sustained release formulations, DoE is widely used to optimize polymer concentration, excipient ratios, and processing conditions to achieve the desired drug release profile [29].

3. Statistical Modeling: Statistical modeling involves the use of mathematical equations and software tools to analyze experimental data generated through DoE. Techniques such as regression analysis and response surface methodology (RSM) help in predicting the effect of formulation and process variables on CQAs. These models enable optimization and establishment of a design space, within which consistent product quality can be assured. Statistical modeling also supports decision-making and regulatory submissions by providing scientific justification for formulation and process choices [29].

6. Application of QbD in Co-Processed Excipients for Sustained Release Tablets

The application of Quality by Design (QbD) in the development of sustained release (SR) tablets using co-processed excipients provides a structured and scientific framework to ensure consistent product quality and performance. This approach emphasizes understanding the relationship between formulation variables and product attributes through a stepwise methodology.

Step 1: Define Quality Target Product Profile (QTPP) The first step in QbD involves defining the Quality Target Product Profile (QTPP), which outlines the desired characteristics of the final product. For sustained release tablets, the QTPP typically includes parameters such as dosage form, route of administration, strength, and most importantly, the drug release profile. For example, a formulation may be designed to release the drug over a period of 12–24 hours to maintain therapeutic drug levels and reduce dosing frequency. Additional considerations such as stability, bioavailability, and patient compliance are also included in the QTPP.

Step 2: Identify Critical Quality Attributes (CQAs) Once the QTPP is established, the next step is to identify Critical Quality Attributes (CQAs). CQAs are the measurable properties of the final product that must be controlled within specific limits to ensure quality. In the case of SR tablets, key CQAs include drug release rate, tablet hardness, friability, and content uniformity. Among these, the drug release profile is the most critical, as it directly influences therapeutic efficacy. Proper identification of CQAs helps in focusing development efforts on attributes that significantly impact product performance.

Step 3: Risk Assessment Risk assessment is conducted to identify and evaluate the variables that may influence the CQAs. This step involves analyzing both material attributes and process parameters. Tools such as Failure Mode and Effects Analysis (FMEA) and Ishikawa diagrams are commonly used to systematically assess risks. For co-processed excipients, factors such as polymer type, excipient ratio, particle size, and moisture content may significantly affect drug release and tablet properties. Similarly, process parameters like mixing time and compression force can also impact the final product. Risk assessment helps prioritize critical variables for further study.

Step 4: Design of Experiments (DoE) Implementation Design of Experiments (DoE) is employed to systematically investigate the effect of selected variables on CQAs. Experimental designs such as factorial design and Box–Behnken design are commonly used in pharmaceutical development. In SR tablet formulation, independent variables may include polymer ratio, concentration of co-processed excipients, and compression force. These variables are studied at different levels to understand their individual and interactive effects on responses such as drug release, hardness, and friability. DoE reduces the number of experimental trials while providing comprehensive data for analysis.

Step 5: Optimization Following DoE, the collected data are analyzed using statistical tools such as response surface methodology (RSM). This step involves developing mathematical models that describe the relationship between independent variables and responses. Optimization is carried out to identify the ideal combination of formulation and process parameters that produce the desired product characteristics. Graphical tools such as contour plots and 3D response surface plots are often used to visualize the design space and select optimal conditions for SR tablet formulation.

Step 6: Validation The final step in the QbD workflow is validation, where the optimized formulation is tested to confirm the reliability of the model predictions. Experimental batches are prepared using the optimized parameters, and the results are compared with predicted values. If the observed results fall within the acceptable range, the model is considered valid. This step ensures that the formulation is robust and reproducible under defined conditions.

9. Advantages of QbD in Sustained Release Tablet Development

Quality by Design (QbD) offers multiple advantages in the development of sustained release (SR) tablets, contributing significantly to the reliability and efficiency of pharmaceutical manufacturing. One of the most prominent benefits is **reduced batch failure**. By identifying critical quality attributes (CQAs) and controlling critical process parameters (CPPs) from the outset, QbD ensures that products consistently meet predefined quality criteria. This systematic approach minimizes the risk of variability between batches and reduces costly product recalls or reformulation efforts [1].

Another key advantage is **regulatory flexibility**. Regulatory authorities, including the FDA and EMA, encourage the use of QbD principles because they provide a thorough scientific rationale for product design and control. Companies implementing QbD can leverage design spaces and control strategies to allow certain operational flexibility without compromising product quality. For example, small adjustments in compression force or polymer ratios can be made within the design space without requiring regulatory resubmission, facilitating efficient manufacturing and scaling [2].

QbD also enhances **product understanding**. The use of risk assessment tools, Design of Experiments (DoE), and statistical modeling provides comprehensive insight into how formulation and process variables interact to affect CQAs. For SR tablets, this ensures predictable drug release profiles, appropriate hardness, and stability, which is especially critical for co-processed excipients where multiple components interact [3].

Finally, QbD enables the development of **robust formulations**. Through systematic optimization and validation, products are less sensitive to minor variations in raw material attributes or process conditions. This robustness is particularly important for SR tablets, as consistent polymer swelling, erosion, and drug release are necessary to maintain therapeutic efficacy. Overall, QbD contributes to higher product quality, regulatory compliance, and reduced development costs.

10. Challenges of Implementing QbD

Despite its benefits, implementing QbD in SR tablet development presents several challenges. One major hurdle is the **complexity in design**. Identifying all critical quality attributes (CQAs), critical material attributes (CMAs), and critical process parameters (CPPs) for co-processed excipients requires a thorough understanding of material science, polymer chemistry, and drug release mechanisms. For multi-component systems, interactions can be unpredictable, demanding sophisticated experimental planning [4].

Another challenge is the **need for statistical expertise**. Tools like Design of Experiments (DoE), response surface methodology (RSM), and regression modeling are central to QbD. Developing, analyzing, and interpreting these models requires specialized knowledge in statistics and experimental design. Pharmaceutical teams may need additional training or consultation with statistical experts, which can increase operational costs [5].

The **time-consuming initial setup** is also a significant consideration. Establishing a QbD framework involves defining QTPP, identifying CQAs, conducting risk assessments, performing multiple DoE studies, and validating models. Compared to traditional trial-and-error methods, this requires substantial upfront investment in terms of planning, experimentation, and documentation.

Moreover, for SR tablets, additional challenges arise due to **complex release mechanisms**. Factors such as polymer swelling, erosion, and drug-polymer interactions introduce variability that must be carefully modeled. Regulatory

acceptance also demands rigorous demonstration of scientific justification for the design space and control strategies. Despite these challenges, the long-term benefits of reduced batch failure, regulatory compliance, and product robustness justify the investment in QbD.

11. Future Perspectives in SR Tablet Development

The future of sustained release tablet development is closely linked to technological innovation, particularly the integration of **artificial intelligence (AI)** in formulation optimization. AI and machine learning can analyze large datasets from DoE experiments and predict optimal polymer ratios, excipient combinations, and processing parameters more efficiently than conventional methods. This accelerates development timelines and enhances precision in achieving target release profiles [6].

Advanced co-processing techniques are expected to further improve excipient functionality. Novel approaches, such as solvent-free co-processing, hot-melt extrusion, and nano-engineered excipients, can enhance compressibility, flow, and drug release control. Such innovations will allow SR tablets to accommodate a broader range of active pharmaceutical ingredients while maintaining high product quality [7].

Continuous manufacturing represents another transformative trend. Unlike batch processing, continuous systems enable real-time monitoring and control, minimizing variability in tablet properties. Integration of QbD principles with continuous manufacturing allows dynamic adjustment of process parameters to maintain consistent CQAs, improving efficiency and reducing waste.

Additionally, the combination of QbD with predictive modeling, real-time release testing, and process analytical technology (PAT) is expected to revolutionize regulatory submissions, moving from prescriptive approaches to science-based, data-driven frameworks. Overall, the convergence of AI, advanced co-processing, and continuous manufacturing is likely to produce SR tablets with higher quality, better reproducibility, and improved patient outcomes.

CONCLUSION

Co-processed excipients have emerged as essential tools in the development of sustained release tablets, providing enhanced compressibility, flow, and stability that are difficult to achieve with conventional excipients alone. Their use, in combination with the structured framework of Quality by Design (QbD), ensures that SR formulations meet precise drug release profiles, mechanical strength, and reproducibility requirements.

QbD allows formulators to systematically understand the influence of material attributes and process parameters, optimize tablet performance, and define a robust design space that mitigates batch-to-batch variability. While the initial setup is complex and resource-intensive, the long-term benefits include reduced batch failures, regulatory flexibility, and enhanced product robustness.

Looking forward, the integration of artificial intelligence, advanced co-processing methods, and continuous manufacturing is poised to transform SR tablet development. These innovations will streamline formulation optimization, improve process efficiency, and expand the applicability of sustained release systems across diverse drug molecules. Overall, the synergy between co-processed excipients and QbD provides a promising pathway for producing high-quality, reproducible, and patient-friendly sustained release tablets.

REFERENCES

1. International Council for Harmonisation. (2009). ICH Q8 (R2): Pharmaceutical development. ICH Harmonised Tripartite Guideline.
2. Singh, B., & Kumar, R. (2013). A review on Quality by Design (QbD) in pharmaceutical development. International Journal of Pharmaceutical Investigation, 3(1), 1–6. https://doi.org/10.4103/2230-973X.108961
3. Gohel, M. C., & Jogani, P. D. (2005). A review of co-processed directly compressible excipients. Journal of Pharmacy and Pharmaceutical Sciences, 8(1), 76–93.
4. Thoorens, G., Krier, F., Leclercq, B., Carlin, B., & Evrard, B. (2014). Microcrystalline cellulose, a direct compression binder in a quality by design environment—A review. International Journal of Pharmaceutics, 473(1–2), 64–72. https://doi.org/10.1016/j.ijpharm.2014.06.055
5. Desai, D., Wong, B., Huang, Y., Ye, Q., Tang, D., Guo, H., & Timmins, P. (2018). Quality by Design approach for development of oral sustained release dosage forms. Asian Journal of Pharmaceutical Sciences, 13(5), 395–407. https://doi.org/10.1016/j.ajps.2017.12.003
6. Rathore, A. S., & Winkle, H. (2009). Quality by Design for biopharmaceuticals. Nature Biotechnology, 27(1), 26–34. https://doi.org/10.1038/nbt0109-26
7. Patel, H., Panchal, D. R., Patel, U., Brahmbhatt, T., & Suthar, M. (2011). Matrix type drug delivery system: A review. Journal of Pharmacy Research, 4(4), 971–976.
8. Nachaegari, S. K., & Bansal, A. K. (2004). Co-processed excipients for solid dosage forms. Pharmaceutical Technology, 28(1), 52–64.
9. Colombo, P., Bettini, R., Santi, P., De Ascentiis, A., Peppas, N. A. (2000). Analysis of the swelling and release mechanisms from drug delivery systems with emphasis on drug solubility and water transport. International Journal of Pharmaceutics, 190(2), 157–171. https://doi.org/10.1016/S0378-5173(99)00227-1
10. Leuenberger, H. (2001). The compressibility and compactibility of powder systems. International Journal of Pharmaceutics, 217(1–2), 1–11. https://doi.org/10.1016/S0378-5173(01)00615-2
11. Siepmann, J., & Siepmann, F. (2012). Modeling of diffusion controlled drug delivery. Journal of Controlled Release, 161(2), 351–362. https://doi.org/10.1016/j.jconrel.2011.10.006
12. Dash, S., Murthy, P. N., Nath, L., & Chowdhury, P. (2010). Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica, 67(3), 217–223.
13. Qiu, Y., Chen, Y., Zhang, G. G. Z., Yu, L., & Mantri, R. V. (2009). Developing solid oral dosage forms: Pharmaceutical theory and practice. Academic Press.
14. Colombo, P., Bettini, R., Santi, P., & Peppas, N. A. (2000). Swellable matrices for controlled drug delivery. Journal of Controlled Release, 39(2–3), 231–237.
15. Siepmann, J., Peppas, N. A. (2001). Modeling of drug release from delivery systems. Advanced Drug Delivery Reviews, 48(2–3), 139–157. https://doi.org/10.1016/S0169-409X(01)00112-7
16. Peppas, N. A., & Narasimhan, B. (2014). Mathematical models in drug delivery. International Journal of Pharmaceutics, 418(1), 6–12.
17. Verma, R. K., & Garg, S. (2001). Current status of drug delivery technologies and future directions. Pharmaceutical Technology, 25(2), 1–14.

18. Thakur, R. R. S., et al. (2013). Functional excipients for oral drug delivery. International Journal of Pharmaceutics, 457(1), 1–12.
19. Leuenberger, H. (2001). The compressibility and compactibility of powder systems. International Journal of Pharmaceutics, 217(1–2), 1–11. https://doi.org/10.1016/S0378-5173(01)00615-2
20. Dressman, J., & Reppas, C. (2000). In vitro–in vivo correlations for lipophilic drugs. European Journal of Pharmaceutical Sciences, 11(Suppl 2), S73–S80.
21. Nachaegari, S. K., & Bansal, A. K. (2004). Co-processed excipients for solid dosage forms. Pharmaceutical Technology, 28(1), 52–64.
22. Gohel, M. C., & Jogani, P. D. (2005). A review of co-processed directly compressible excipients. Journal of Pharmacy and Pharmaceutical Sciences, 8(1), 76–93.
23. Thoorens, G., Krier, F., Leclercq, B., Carlin, B., & Evrard, B. (2014). Microcrystalline cellulose, a direct compression binder in a quality by design environment. International Journal of Pharmaceutics, 473(1–2), 64–72. https://doi.org/10.1016/j.ijpharm.2014.06.055
24. Desai, D., Wong, B., Huang, Y., Ye, Q., Tang, D., Guo, H., & Timmins, P. (2018). Quality by Design approach for pharmaceutical development. Asian Journal of Pharmaceutical Sciences, 13(5), 395–407. https://doi.org/10.1016/j.ajps.2017.12.003
25. International Council for Harmonisation. (2009). ICH Q8 (R2): Pharmaceutical development.
26. Rathore, A. S., & Winkle, H. (2009). Quality by Design for biopharmaceuticals. Nature Biotechnology, 27(1), 26–34. https://doi.org/10.1038/nbt0109-26
27. Yu, L. X. (2008). Pharmaceutical quality by design: Product and process development, understanding, and control. Pharmaceutical Research, 25(4), 781–791. https://doi.org/10.1007/s11095-007-9511-1
28. Thoorens, G., et al. (2014). Microcrystalline cellulose in a QbD environment. International Journal of Pharmaceutics, 473(1–2), 64–72. https://doi.org/10.1016/j.ijpharm.2014.06.055
29. Montgomery, D. C. (2017). Design and analysis of experiments (9th ed.). Wiley.

HOW TO CITE: Darshana Deshmukh, Milke R, Co-Processed Excipients in Sustained Release Tablet: A Quality by Design-Based Review, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 5, 936-948, https://doi.org/10.5281/zenodo.20038628