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Review Article

Formulation, Evaluation and Optimization of Metformin Hydrochloride 500 mg Sustained-Release Tablets Using a Quality-By-Design Approach: A Comprehensive Review

Rahul Dev [1], Dharmendra Sahu [1], Ruchi Gupta [1], Niharika Sahu [2], Rupesh Sahu [3], Shiv Kumar Bhardwaj [3*]

[1] Gracious College of Pharmacy, Village-Belbhata, Abhanpur, Raipur-493661, Chhattisgarh, India

[2] Columbia College of Pharmacy, Columbia Professional University, Tekari, Near Vidhansabha Road, Raipur-493111, Chhattisgarh, India

[3] Columbia Institute of Pharmacy, Columbia Professional University, Tekari, Near Vidhansabha Road, Raipur-493111, Chhattisgarh, India

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For Correspondence:

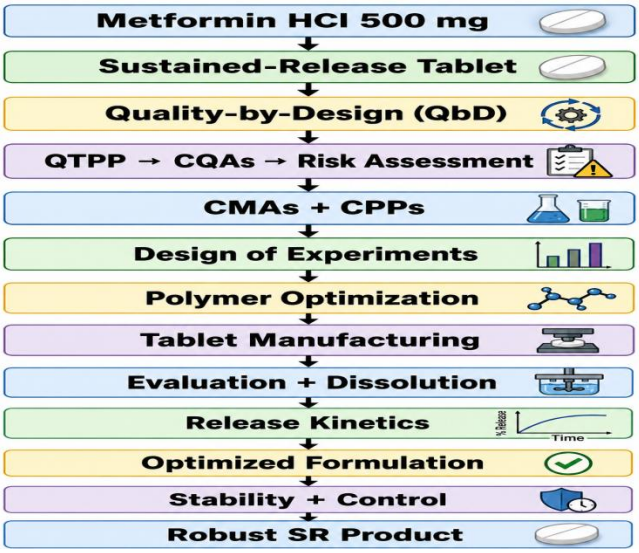
Shiv Kumar Bhardwaj, Columbia Institute of Pharmacy, Columbia Professional University, Tekari, Near Vidhansabha Road, Raipur-493111, Chhattisgarh, India.

Abstract

Metformin hydrochloride is a first-line oral antihyperglycemic agent widely used for the management of type 2 diabetes mellitus. Despite its therapeutic effectiveness, its high aqueous solubility, relatively limited membrane permeability, dose-related gastrointestinal effects and restricted intestinal absorption window can complicate the development of prolonged-release oral formulations. Sustained-release (SR) matrix tablets provide a rational strategy for controlling drug release, reducing dosing frequency, improving dosing convenience and maintaining more consistent systemic exposure. This review presents a Quality-by-Design (QbD)-oriented framework for the formulation, evaluation and optimization of 500-mg metformin hydrochloride SR matrix tablets. The framework incorporates the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQAs), Critical Material Attributes (CMAs), Critical Process Parameters (CPPs), risk assessment, Design of Experiments (DoE), formulation optimization and lifecycle control. Particular emphasis is placed on hydrophilic matrix systems containing hydroxypropyl methylcellulose (HPMC), together with the roles of hydrophobic and natural polymers and functional excipients. Key formulation and process variables, including polymer concentration, viscosity grade, drug-to-polymer ratio, compression force, porosity and manufacturing conditions, are considered in relation to matrix hydration, gel formation, diffusion, erosion and drug-release behavior. Evaluation includes pre-formulation, powder properties, tablet quality, assay, content uniformity, compatibility, swelling, dissolution, release kinetics and stability. Emerging tools such as process analytical technology, physiologically based biopharmaceutic modeling, artificial intelligence, machine learning and continuous manufacturing may further enhance predictive development, robustness, scalability, and lifecycle control of metformin SR tablets.

Keywords: Metformin Hydrochloride; Sustained-Release Tablets; Quality By Design; Design Of Experiments; Matrix Tablets.

Graphical abstract



Highlights

✓QbD provides a systematic framework for metformin SR tablet development.

✓Polymer concentration and viscosity strongly influence drug-release behavior.

✓DoE enables systematic formulation and process optimization.

✓Comprehensive evaluation establishes tablet quality and release performance.

AI, machine learning, PBBM, PAT and continuous manufacturing provide opportunities for predictive development.

1. Introduction

Metformin hydrochloride is a widely used biguanide antihyperglycemic drug for the treatment of type 2 diabetes mellitus. Its primary glucose-lowering effect is attributed to suppression of hepatic glucose production, along with effects on peripheral glucose utilization and gastrointestinal mechanisms.[1] Despite its established efficacy, metformin presents formulation challenges because of its high aqueous solubility and relatively low intestinal permeability. It is generally classified as a Biopharmaceutics Classification System (BCS) Class III drug. Rapid dissolution after gastrointestinal exposure therefore makes controlled drug release difficult.[2] Sustained-release (SR) formulations are developed to prolong drug release, reduce dosing frequency and improve patient convenience. Hydrophilic matrix tablets containing hydroxypropyl methylcellulose (HPMC) are widely investigated for this purpose. HPMC hydrates in gastrointestinal fluid and forms a viscous gel barrier through which dissolved metformin diffuses. Drug release is influenced by polymer concentration and viscosity, drug loading, tablet porosity, compression force and manufacturing conditions.[3] Quality by Design (QbD) provides a systematic approach to formulation development by integrating predefined product objectives, risk assessment, Design of Experiments (DoE) and process understanding. For metformin SR tablets, QbD establishes relationships among the Quality Target Product Profile, Critical Quality Attributes, Critical Material Attributes and Critical Process Parameters. This approach facilitates optimization and supports development of robust, reproducible 500-mg metformin hydrochloride SR tablets.[4]

2. Pharmaceutical and biopharmaceutical characteristics of metformin hydrochloride

Metformin hydrochloride is a hydrophilic biguanide compound characterized by high aqueous solubility and comparatively low membrane permeability. These characteristics strongly influence the design of modified-release dosage forms. High solubility represents a major formulation challenge because dissolved drug can rapidly migrate through a hydrated polymeric matrix. Therefore, the release-controlling polymer must create adequate diffusional resistance without preventing complete drug release.[5] Metformin is generally classified as a BCS Class III drug because of high solubility and low permeability. Consequently, both dissolution and permeability should be considered when interpreting the performance of an SR formulation.[6]

Table 1. Pharmaceutical and biopharmaceutical characteristics of metformin hydrochloride[7–9]

Characteristic	Description	Formulation relevance
Active ingredient	Metformin hydrochloride	Therapeutic API
Strength	500 mg	Determines drug loading
Drug class	Biguanide antihyperglycemic	Therapeutic application
Aqueous solubility	High	May promote rapid dissolution
BCS classification	Class III	High solubility and low permeability
Intestinal permeability	Relatively low	Important for absorption
Main formulation challenge	Controlled release of soluble drug	Requires effective matrix
Preferred approach	Polymeric matrix system	Controls drug diffusion
Major release mechanisms	Diffusion, swelling, gel formation, erosion	Determines dissolution behavior

3. Rationale and advantages of sustained-release metformin tablets

The primary objective of metformin hydrochloride SR tablets is to achieve controlled and prolonged drug release with consistent tablet quality. Since metformin is highly water soluble, controlled water penetration, polymer hydration, swelling, gel formation and drug diffusion are essential to prevent rapid release. SR formulations can reduce dosing frequency, improve convenience and adherence and provide predictable drug release.[10] Drug-release behavior depends on polymer type and concentration, viscosity, tablet porosity, compression force, hydration, diffusion, and erosion. An optimized formulation should provide a balanced and reproducible release profile, avoid excessive initial release and maintain matrix integrity,

mechanical strength, manufacturing consistency and stability.[11]

4. Quality-By-Design (QbD) framework for metformin sustained-release tablets

QbD begins with predefined product objectives and establishes relationships among formulation composition, manufacturing process, product attributes and performance.

4.1 Quality target product profile (QTPP)

Quality Target Product Profile (QTPP) defines the desired quality safety, efficacy and performance of a metformin hydrochloride 500-mg SR tablet. It includes an oral sustained-release dosage form, 500-mg strength, acceptable appearance, consistent assay and content uniformity, adequate hardness and low friability, controlled and reproducible drug release, and satisfactory physical and chemical stability throughout the shelf life. These targets guide the identification of CQAs, CMAs and CPPs and support development of an effective formulation and process control strategy.[12]

4.2 Critical quality attributes (CQA)

Critical Quality Attributes (CQAs) are the physical, chemical and performance characteristics that must remain within predefined limits to ensure the quality and performance of metformin hydrochloride 500-mg SR tablets. Key CQAs include appearance, weight, thickness, hardness, friability, assay, content uniformity, moisture content, dissolution, drug-release kinetics and stability**.** Among these, dissolution is particularly critical because it determines the controlled and sustained drug-release performance of the formulation.[13]

4.3 Critical material attributes (CMA)

Critical Material Attributes (CMAs) are the physical, chemical and functional properties of the API and excipients that influence the CQAs of metformin hydrochloride SR tablets. Key CMAs include polymer type, concentration, viscosity grade, drug and excipient particle size, binder and lubricant concentration, moisture content and excipient functionality. Among these, polymer characteristics are most critical because they control matrix formation, hydration, gel strength, drug diffusion and the dissolution profile.[14]

4.4 Critical process parameters (CPP)

Critical Process Parameters (CPPs) are manufacturing variables that can significantly affect the CQAs and performance of metformin hydrochloride SR tablets. Key CPPs include mixing time and speed, granulation endpoint, binder addition, drying temperature and time, residual moisture, milling, lubrication time, compression force and compression speed**.** These parameters influence blend uniformity, granule properties, tablet porosity, mechanical strength, polymer distribution and drug-release profile**.** CPPs should therefore be identified through risk assessment and systematically evaluated to establish a robust and reproducible manufacturing process.[15]

4.5 Risk Assessment

Risk assessment can be performed using: Failure mode and effects analysis, ishikawa diagram, risk-ranking matrix, cause-and-effect analysis, hazard analysis.[16] Figure 1. QbD framework for the development of metformin hydrochloride 500-mg SR tablets. The figure illustrates the sequential integration of QTPP, CQAs, risk assessment, CMAs, CPPs, DoE, formulation optimization, design space, evaluation, control strategy, and lifecycle management**.** Figure 1 QbD-based development and optimization of metformin 500 mg sustained-release tablets.

The figure illustrates the systematic progression from QTPP and CQAs through risk assessment, DoE, formulation optimization, and design space, leading to the optimized product, followed by evaluation, control strategy and lifecycle management.

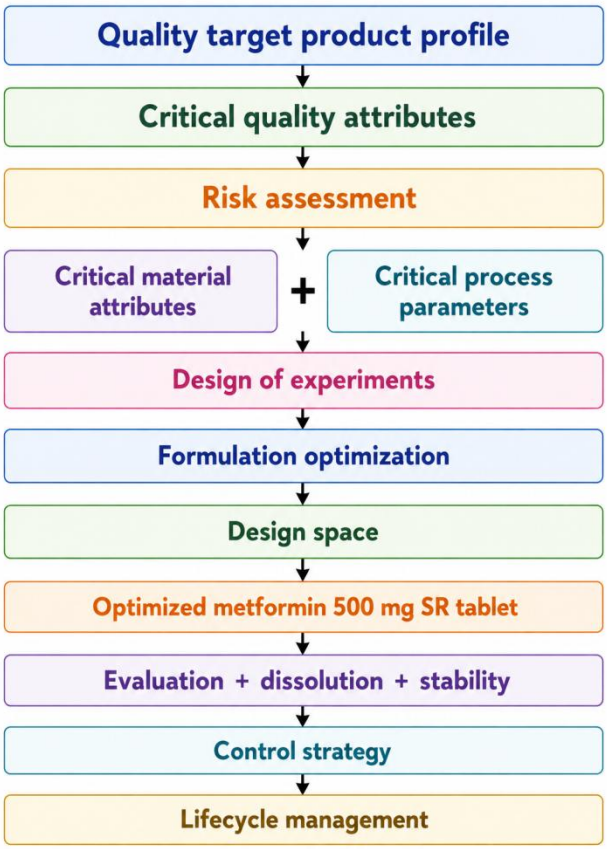


Figure 1. Flow diagram represents various steps involved in QbD framework for metformin 500 mg SR tablet development

(Integrated QbD pathway connecting product objectives, risk assessment, material and process variables, optimization, evaluation, control strategy and lifecycle management).

Table 2. QTPP, CQAs, CMAs and CPPs for metformin SR tablets[17–22]

QbD Component	Example	Importance
QTPP	500-mg oral SR tablet	Defines target product
CQA	Dissolution	Determines release performance
CQA	Assay	Ensures drug-content accuracy
CQA	Content uniformity	Ensures dose consistency
CQA	Friability	Indicates mechanical integrity
CMA	Polymer concentration	Controls release rate
CMA	Polymer viscosity	Influences gel strength
CMA	Binder concentration	Influences matrix structure
CPP	Mixing time	Affects blend uniformity
CPP	Granulation endpoint	Affects granule properties
CPP	Drying conditions	Affects moisture
CPP	Compression force	Affects hardness and porosity
CPP	Lubrication time	May affect tablet ability and wetting

5. Formulation strategies and polymer selection

Polymer selection is a major determinant of sustained-release performance because polymers influence water penetration, hydration, swelling, gel strength, diffusion and erosion.

5.1 HPMC

Hydroxypropyl methylcellulose (HPMC) is a widely used hydrophilic matrix-forming polymer for sustained-release tablets. On contact with aqueous media, HPMC hydrates and forms a viscous gel layer that controls metformin release by increasing diffusional resistance. Higher polymer concentrations generally strengthen the gel and may prolong drug release. Different viscosity grades, such as HPMC K4M, K15M and K100M, can produce different release profiles due to differences in hydration and gel formation. For 500-mg metformin hydrochloride SR tablets, HPMC K15M has been reported as an important formulation variable influencing drug release, highlighting its significance in formulation optimization.[23]

5.2 PVP

Polyvinylpyrrolidone (PVP), particularly PVP K30**,** is commonly used as a binder in matrix-tablet formulations. It improves granule formation, compressibility and mechanical properties and may also influence matrix porosity and, consequently, drug dissolution and release. PVP K30 has been investigated in combination with HPMC K15M in optimized 500-mg metformin hydrochloride sustained-release formulations, supporting its relevance as a formulation variable in the development of metformin SR tablets.[24]

5.3 Ethyl cellulose

Ethyl cellulose is a hydrophobic polymer that can reduce water penetration into the tablet matrix and retard drug diffusion. It may be used independently or in combination with hydrophilic polymers such as HPMC to modify and control the drug-release profile**.**[25]

5.4 Natural polymers

Natural polymers such as xanthan gum and guar gum can form hydrated matrices and retard drug diffusion, making them useful as natural release-controlling agents in sustained-release formulations. However, their performance may be affected by source variability, viscosity variation, hydration characteristics, microbial quality and compositional variability**;** therefore, these attributes should be carefully controlled to ensure consistent formulation performance.[26]

5.5 Polymer combinations

Combining hydrophilic and hydrophobic polymers can provide greater flexibility in controlling the drug-release profile. Such combinations can modulate water penetration, polymer swelling, drug diffusion and matrix erosion, thereby enabling more precise control of sustained drug release.[27]

Table 3. Polymers and their role in sustained drug release

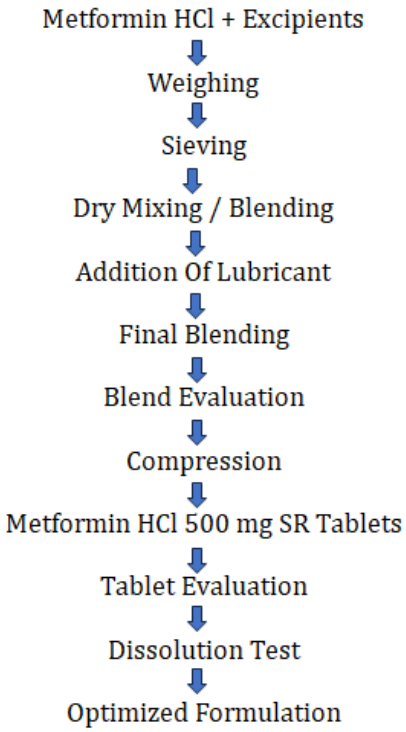
Polymer	Type	Major function	Expected effect	ReF.
HPMC	Hydrophilic	Gel/matrix formation	Retards drug diffusion	28
PVP K30	Hydrophilic binder	Binding and granulation	Modifies matrix structure	29
Ethyl cellulose	Hydrophobic	Diffusion barrier	Reduces water penetration	30
Xanthan gum	Natural hydrophilic	Swelling and gel formation	Retards release	31
Guar gum	Natural hydrophilic	Matrix formation	Controls diffusion	32
Polymer combinations	Mixed	Combined release control	Enables profile optimization	33

6. Manufacturing methods and critical process parameters

The manufacturing process influences granule properties, tablet density, porosity, mechanical strength, polymer distribution and drug-release behavior.

6.1 Direct compression[34]

Direct compression involves blending the API and excipients followed by compression into tablets without an intermediate granulation step. It is a simple manufacturing approach, but successful production requires adequate powder flow, minimal segregation, good compressibility, blend uniformity and uniform polymer distribution to ensure consistent tablet quality and reproducible sustained drug-release performance.



Advantages[35]

✓ Simple process.

✓ Fewer manufacturing steps.

✓ Lower processing time.

✓ Suitable for direct-compression excipients.

Critical Considerations[36]

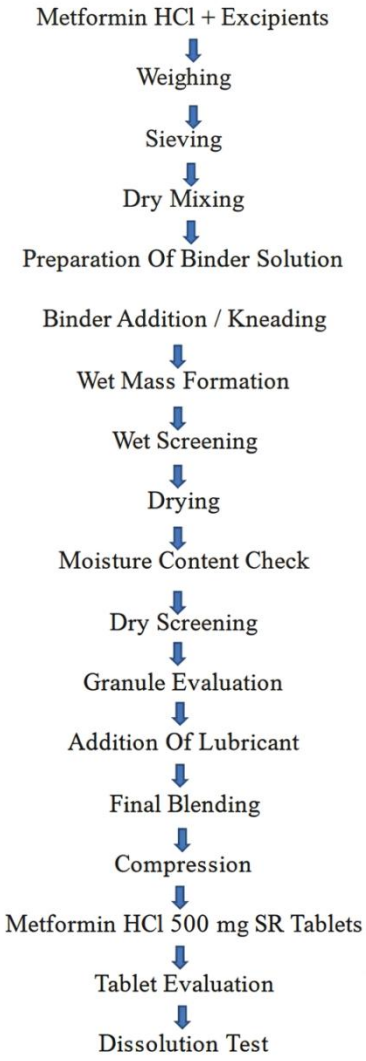
✓ Powder flow.

✓ Segregation.

✓ Compressibility.

✓ Uniform distribution of polymer.

✓ Drug-content uniformity.



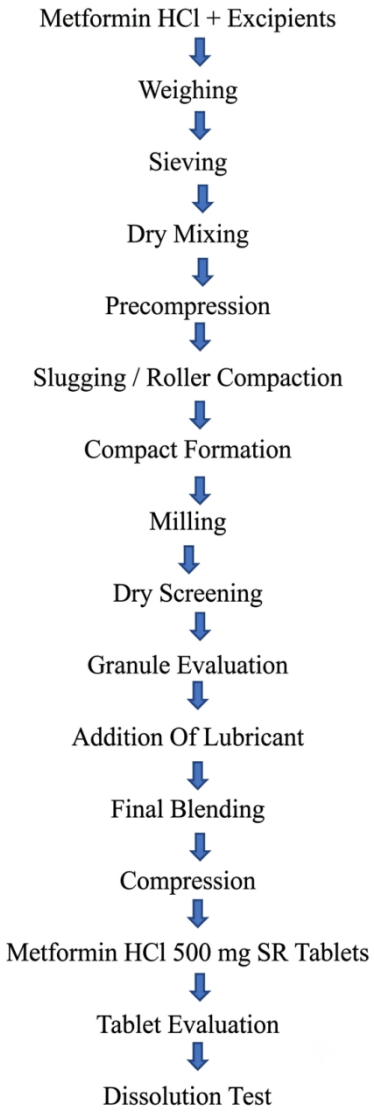
6.2 Wet granulation[37]

Wet granulation is widely used to improve powder flow, compressibility and blend uniformity by forming granules. The process includes binder addition, granulation, drying, sizing, lubrication and compression.

Key process variables include binder concentration, addition rate, granulation time and endpoint, drying temperature and time, residual moisture and milling conditions. Proper control of these variables is essential because they affect granule properties, tablet porosity, mechanical strength and ultimately the sustained-release profile of metformin hydrochloride tablets.

6.3 Dry granulation[38]

Dry granulation may be useful when moisture exposure is undesirable. Roller compaction or slugging can produce compacted material that is subsequently milled and compressed.



6.4 Compression parameters

Compression force is a critical process parameter affecting tablet hardness, porosity, thickness, mechanical strength, water penetration, polymer hydration and drug release. Higher compression force generally produces harder, less porous tablets, which may slow hydration and drug diffusion. Insufficient compression can result in weak tablets, capping, chipping and increased friability. Therefore, an optimum compression force should be established to balance mechanical strength and the desired sustained-release profile.[39]

7. Design of experiments and formulation optimization

DoE allows several formulation and process variables to be investigated simultaneously and provides information regarding main effects, interactions and nonlinear relationships.

7.1 Factorial design

Factorial design is a Design of Experiments (DoE) approach in which multiple formulation or process variables are investigated simultaneously at predefined levels. It is particularly useful for screening important factors during early formulation development, identifying their individual effects and interactions and determining which variables require further optimization. In metformin SR tablet development, factors such as polymer concentration, binder concentration, compression force, or other critical formulation variables can be systematically evaluated against responses such as hardness, friability, swelling and drug release.[40]

7.2 Box-Behnken design

Box–Behnken Design (BBD) is a Response Surface Methodology (RSM) used to study the effects of multiple formulation or process variables. It evaluates linear, interaction and quadratic effects with fewer experimental runs than many full factorial designs. In metformin SR tablet development, BBD can optimize factors such as polymer concentration, binder concentration and compression force and evaluate their effects on drug release, hardness, friability and swelling index.[41]

7.3 Central composite design

Central composite design (CCD) is a Response Surface Methodology (RSM) used for formulation optimization. It evaluates linear, interaction and quadratic effects of formulation and process variables on product responses. In metformin SR tablet development, CCD can optimize factors such as polymer concentration, binder concentration and compression force against responses including drug release, hardness, friability and swelling behavior, helping identify optimal formulation and process conditions.[42]

7.4 Response-surface methodology

For metformin hydrochloride SR tablets, HPMC concentration, PVP concentration, hydrophobic-polymer concentration, and compression force can be selected as independent variables for DoE-based optimization. Their effects can be assessed using responses such as drug release at selected time points, T_{50}%, hardness, friability, and swelling index. These variables and responses help establish the relationship between formulation composition, manufacturing conditions, tablet properties, and sustained-release performance.[43]

7.5 Desirability-based optimization

A desirability function can simultaneously optimize multiple formulation responses by combining individual

responses to identify the best overall formulation. For metformin SR tablets, objectives include minimizing initial burst release, achieving desired drug release, maintaining adequate hardness, and minimizing friability. The predicted optimized formulation should be prepared and experimentally evaluated, and the observed results compared with predicted values to validate the optimization model.[44]

8. Evaluation and characterization of metformin SR tablets

Evaluation should comprehensively cover precompression properties, post compression properties, drug content, compatibility, solid-state characterization, swelling, dissolution, release kinetics, and stability.

8.1 Precompression evaluation

Angle of repose

Angle of repose is a precompression parameter used to evaluate powder flowability. A lower angle generally indicates better flow, although the result depends on the powder properties and measurement method.[45]

$$\theta = tan^{-1}\frac{r}{h}$$

Where:

θ = Angle of repose

h = Height of the powder heap

r = Radius of the powder heap

Alternatively, when diameter D is measured:

$$\theta = tan^{-1}\frac{2h}{D}$$

Interpretation: A lower angle generally indicates better powder flow.

Bulk density

Bulk density represents the mass of powder occupying a given bulk volume before tapping.[46]

$$\text{Bulk Density} = \frac{\text{Bulk Volume}}{\text{Weight of Powder}}$$

Tapped density

Tapped density is the mass of powder divided by its volume after standardized tapping. It indicates the packing characteristics, flowability and compressibility of the powder before tablet compression.[47]

$$\text{Tapped Density} = \frac{\text{Tapped Volume}}{\text{Mass of Powder}}$$

Where:

Mass of powder = weight of the powder sample

Tapped volume = volume occupied by the powder after standardized tapping

Carr's compressibility index

Carr's compressibility index is a precompression parameter used to evaluate powder flow and compressibility based on the difference between bulk density and tapped density.[48]

$$\text{Carr's Index (\%)} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

Where:

Tapped Density = density after standardized tapping

Bulk Density = density before tapping

Hausner ratio

Hausner ratio is a precompression parameter used to evaluate powder flowability and interparticle friction. It is calculated from the ratio of tapped density to bulk density.[49]

$$\text{Hausner Ratio} = \frac{\text{Bulk Density}}{\text{Tapped Density}}$$

Where:

Tapped Density = density after standardized tapping

Bulk Density = density before tapping

Moisture content

Moisture content is a precompression parameter that measures the amount of water present in powders or granules. It can affect flow, granule strength, compressibility, polymer hydration, tablet stability and drug-release behavior.[50]

$$\text{Moisture Content (\%)} = \frac{\text{Initial Weight} - \text{Final Dry Weight}}{\text{Initial Weight}} \times 100$$

Where:

Initial Weight = weight of sample before drying

Final Dry Weight = weight of sample after drying to constant weight

Particle-size distribution

Particle size is an important pre-formulation parameter that affects powder flow, packing, blend uniformity, compressibility, surface area and dissolution. Differences in particle size can cause segregation and dose-uniformity issues, while changes in surface area may alter drug dissolution. Therefore, controlled particle-size distribution is essential for consistent manufacturing and reproducible drug release.[51]

8.2 Post-compression evaluation

Appearance

Visual inspection of tablets is performed to assess color, shape, surface defects, capping, cracking, chipping, lamination and mottling. It provides a preliminary indication of tablet quality, manufacturing consistency and physical integrity.[52]

Weight Variation

Weight variation is evaluated by weighing individual tablets and comparing them with the mean tablet weight. It assesses weight uniformity and manufacturing consistency and helps detect variations during feeding, blending, granulation or compression.[53]

Thickness

Tablet thickness is measured using a calibrated thickness gauge or vernier caliper to assess dimensional uniformity. It is influenced by compression force, tablet weight, punch geometry, and granule properties. Consistent thickness indicates uniform tablet quality and reproducible manufacturing performance.[54]

Diameter

For round tablets, diameter should remain consistent within the specified manufacturing tolerance to ensure dimensional uniformity and reproducible tablet quality. Variations in diameter may indicate inconsistencies in tablet compression, granule properties, or manufacturing conditions[55]

Hardness

Tablet hardness is the resistance of a tablet to mechanical deformation during handling, packaging, transportation, and storage. Excessive hardness may reduce porosity and water penetration, delaying polymer hydration and drug release. Therefore, an appropriate hardness range should balance mechanical strength and desired dissolution performance.[56]

Friability

Friability measures the resistance of tablets to abrasion and mechanical stress during handling, packaging, and transportation. Hardness and friability should be evaluated together because adequate mechanical strength alone does not establish the sustained-release performance of the formulation. An appropriate balance between tablet strength, friability, porosity and drug-release behavior is therefore required. It is calculated as:[57]

$$\text{Friability (\%)} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

8.3 Assay

Assay determines the amount of metformin hydrochloride present in the finished tablet and confirms the drug content. Common methods include UV–visible spectrophotometry and HPLC. HPLC offers greater specificity when separating metformin from excipients, impurities, or degradation products. The analytical method should demonstrate specificity, accuracy, precision, linearity, range and robustness for reliable drug quantification.[58]

8.4 Content uniformity

Content uniformity determines the metformin hydrochloride content in individual tablets and assesses dose consistency. It involves individual tablet analysis, mean content calculation, variability assessment and comparison with pharmacopoeial acceptance criteria. This ensures uniform and accurate drug delivery from each SR tablet.[59]

8.5 FTIR compatibility study

FTIR spectroscopy is used to assess potential drug-excipient interactions in metformin SR formulations. Spectra of the pure drug, excipients, physical mixture and optimized formulation are compared for changes in characteristic peaks. Retention of major peaks generally indicates compatibility, while new peaks, major shifts, or disappearance of peaks may suggest interactions. However, minor peak shifts should be interpreted with complementary techniques such as DSC and XRD.[60]

8.6 Differential scanning calorimetry

Differential scanning calorimetry (DSC) evaluates the melting behavior, thermal transitions, crystallinity, drug–excipient interactions and physical-state changes of metformin hydrochloride formulations. Comparing the pure drug, physical mixture and optimized formulation helps detect significant thermal changes and provides evidence of drug–excipient compatibility and solid-state stability.[61]

8.7 X-Ray Diffraction

X-ray diffraction (XRD) is used to characterize the crystalline or amorphous nature of metformin hydrochloride and the optimized formulation. Changes in diffraction patterns may indicate reduced crystallinity, amorphization, polymorphic transformation, or other solid-state changes.[62]

8.8 Swelling Index

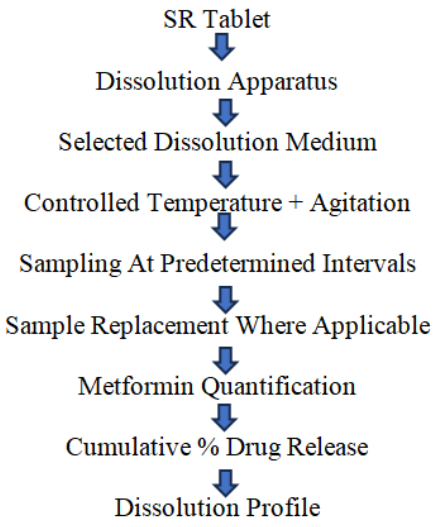
Swelling studies are particularly important for hydrophilic matrix tablets because they assess the ability of the polymer to absorb water and form a hydrated gel layer. The swelling index is calculated as:[63]

$$\text{Swelling Index (\%)} = \frac{Wt - W0}{W0} \times 100$$

where **W0** is the initial tablet weight and Wt is the weight of the hydrated tablet at time t. Swelling studies provide information about water uptake, polymer hydration, gel formation, and matrix integrity, which are important factors governing the sustained-release behavior of metformin tablets.

8.9 *In-Vitro* dissolution testing

Dissolution testing is the most important performance evaluation for SR tablets because it determines the rate and extent of metformin release. A suitable method should be reproducible, discriminatory and scientifically justified. Tablets are placed in a suitable dissolution apparatus and medium under controlled temperature and agitation. Samples are withdrawn at predetermined intervals and analyzed using a validated method. Cumulative drug release is calculated and plotted against time. Sampling should cover the initial, intermediate and final stages to adequately characterize the complete SR profile.[64]



8.10 Dissolution-profile comparison

Dissolution profiles of metformin hydrochloride SR tablets can be evaluated using cumulative drug release, difference factor (f_1), similarity factor (f_2), model-independent methods and kinetic models. The f_1 factor measures the percentage difference between test and reference profiles, while the f_2 factor assesses the similarity or closeness of the two dissolution profiles.[65]

The similarity factor is calculated as:

$$f2=50\log\{1+n1t=1\sum n(Rt-Tt)2\}-0.5\times100$$

where $\mathbf{R_t}$ represents the reference dissolution value, $\mathbf{T_t}$ represents the test dissolution value at time point *t* and **n** is the number of sampling points. A higher f_2 value indicates greater similarity, while f_1 indicates the difference between dissolution profiles. These factors, along with release-kinetic models, help characterize and compare the performance of metformin SR formulations.

Table 4. Evaluation parameters and their scientific significance[66–70]

Evaluation parameter	Scientific significance
Angle of repose	Powder-flow assessment
Bulk density	Powder-packing behavior
Tapped density	Packing after tapping
Carr's index	Compressibility/flow
Hausner ratio	Interparticle friction/flow
Particle size	Flow, packing and dissolution
Moisture content	Stability and processing
Appearance	Visible tablet quality
Weight variation	Manufacturing consistency
Thickness	Dimensional uniformity
Diameter	Dimensional consistency
Hardness	Mechanical strength
Friability	Abrasion resistance
Assay	Overall drug content
Content uniformity	Unit-to-unit dose consistency
FTIR	Drug–excipient compatibility
DSC	Thermal characterization
XRD	Solid-state characterization
Swelling index	Matrix hydration
Dissolution	Drug-release performance
Release kinetics	Mechanistic interpretation
Stability	Quality during storage

9. Dissolution, drug-release kinetics and mechanism

Drug release from hydrophilic metformin matrix tablets generally involves several interconnected mechanisms.

Water penetration

Water penetration is the initial step in drug release from a hydrophilic matrix tablet. It allows the dissolution medium to enter the tablet, promoting polymer hydration, swelling, and gel-layer formation. The rate of water penetration subsequently influences metformin diffusion and drug release.[71]

Polymer hydration

Hydrophilic polymers absorb water and hydrate, causing swelling and formation of a hydrated gel layer. This gel barrier controls water penetration and metformin diffusion, thereby providing sustained drug release.[72]

Matrix swelling

Hydration causes polymer swelling and matrix expansion, increasing the gel-layer thickness and helping control water penetration and metformin diffusion.[73]

Gel-layer formation

A viscous gel layer forms around the hydrated tablet, creating diffusional resistance that controls metformin movement into the dissolution medium and provides sustained drug release.[74]

Drug dissolution

Metformin dissolves within the hydrated polymer matrix and then diffuses through the gel layer into the surrounding dissolution medium, contributing to controlled drug release.[75]

Drug diffusion

Dissolved metformin diffuses through the hydrated polymer gel layer into the dissolution medium. The gel acts as a diffusional barrier, slowing drug movement and providing controlled, sustained release.[76]

Polymer relaxation and erosion

Continued hydration causes polymer relaxation and gradual matrix erosion, reducing diffusional resistance and promoting the further release of metformin from the SR tablet.[77] Figure 2. Mechanism of controlled drug release from metformin SR matrix tablets.

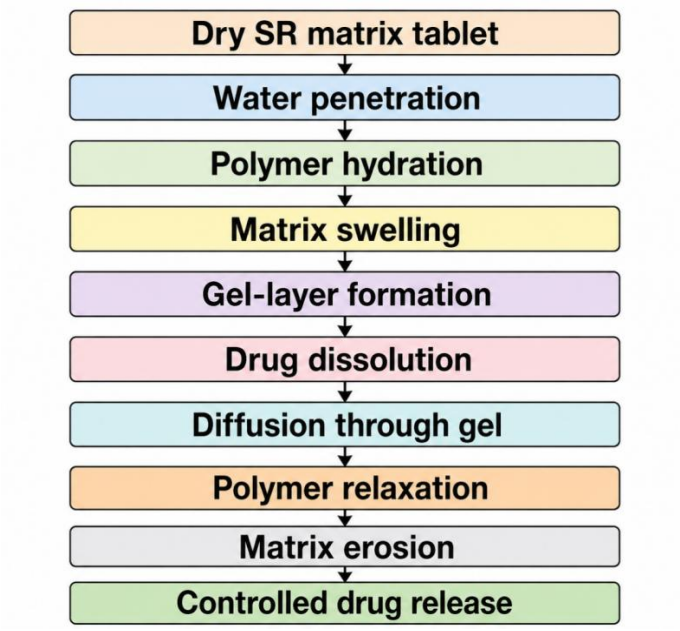


Figure 2. Mechanism of metformin release from hydrophilic matrix tablet

(Sequential representation of hydration, swelling, gel formation, diffusion, polymer relaxation, and erosion during metformin release.)

Drug-release kinetic analysis

Zero-order model

$$Qt = Q0 + K0t$$

The zero-order model describes relatively constant drug release with time, indicating that the release rate is largely independent of the amount of drug remaining in the dosage form.[78]

First-order model

The first-order model describes drug release according to the amount of drug remaining in the dosage form, with the release rate decreasing as the amount of unreleased drug decreases.[79]

Higuchi model

$$Q = K_H\sqrt{t}$$

The Higuchi model describes diffusion-controlled drug release from matrix systems, where the amount of drug released is proportional to the square root of time.[80]

Korsmeyer-peppas model

$$\frac{Mt}{M\infty} = Ktn$$

where Mt/M∞ represents the fraction of drug released at time t, K is the release-rate constant, and n provides information about the release mechanism. Interpretation of n depends on the dosage-form geometry and assumptions of the model.[81]

Table 5. Drug-release models and their interpretation

Model	Mathematical expression	Main interpretation
Zero-order	Qt=Q0+K0t	Constant release rate
First-order	Log-based release relationship	Release related to drug remaining
Higuchi	Q=KHt	Diffusion-controlled release
Korsmeyer-Peppas	Mt/M∞=Ktn	Mechanistic release assessment

10. Stability, analytical method validation and regulatory considerations

Stability studies

Stability studies determine whether the optimized metformin SR formulation maintains its physical, chemical and performance characteristics during storage. Key parameters include appearance, assay, dissolution, hardness, friability, moisture content, degradation products and physical characteristics.[82]

Analytical method validation

Analytical methods for assay and dissolution should be fit for their intended purpose and demonstrate specificity, accuracy, precision, linearity and range, robustness and suitable detection/quantitation capability.[83]

Regulatory Considerations

The QbD framework incorporates ICH Q8 for Pharmaceutical Development, ICH Q9 for Quality Risk Management, ICH Q10 for the Pharmaceutical Quality System, ICH Q14 for Analytical Procedure Development, ICH Q2(R2) for Analytical Procedure Validation, and ICH Q1A for Stability Testing. These guidelines support systematic development, risk management, analytical control and product stability. The overall control strategy can be represented as:[84]

Raw Material Control → Process Control → In-Process Testing → Finished Product Testing → Stability Monitoring → Lifecycle Management

11. Advanced approaches: AI, machine learning, PBBM, PAT and continuous manufacturing

Artificial intelligence and machine learning can complement conventional statistical methods when formulation behavior is nonlinear.

Artificial neural networks

Artificial neural network (ANN) models can be used to capture nonlinear relationships between formulation variables and dissolution responses, making them useful for predicting drug-release behavior and supporting formulation optimization of metformin hydrochloride SR tablets.[85]

Machine learning

Machine-learning algorithms can analyze formulation, process and dissolution datasets to predict product performance, identify influential variables and support data-driven optimization of metformin hydrochloride SR tablet formulations.[86]

Physiologically based biopharmaceutic modeling(PBBM)

Physiologically based biopharmaceutic modeling (PBBM) can integrate in-vitro dissolution data with gastrointestinal physiology and pharmacokinetic behavior, helping predict how formulation-dependent drug release may influence in-vivo drug exposure and support formulation optimization.[87]

Process analytical technology

Process analytical technology (PAT) enables real-time or near-real-time monitoring of critical material attributes and process parameters during manufacturing. In metformin SR tablet development, PAT can be applied to monitor blend uniformity, moisture content, granule properties, compression behavior and tablet characteristics, helping detect process variability and maintain consistent product quality.[88]

Continuous manufacturing

Continuous manufacturing integrates material feeding, blending, granulation, drying and compression into an interconnected production process. This approach can improve process consistency, reduce process variability, enable continuous monitoring and support more efficient manufacturing of metformin hydrochloride sustained-release tablets. Figure 3. Integrated QbD–DoE–AI/ML framework for predictive optimization and lifecycle management of metformin SR tablets.[89]

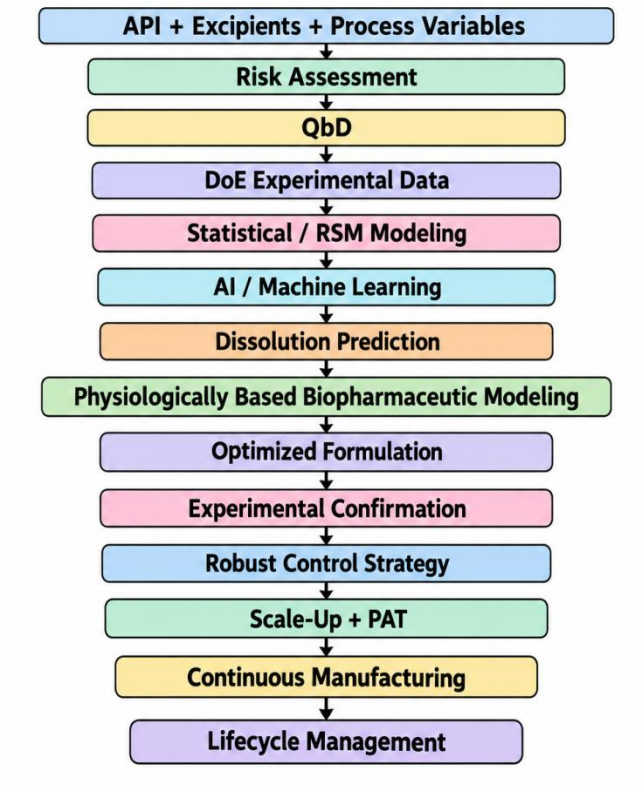


Figure 3. Flow diagram represents various steps involved in integrated DoE–QbD–AI-based optimization strategy

(Integrated QbD, DoE, statistical modeling, AI/ML, dissolution prediction, PBBM, PAT and continuous manufacturing strategy for predictive optimization).

12. Future perspectives

Future development of metformin hydrochloride SR tablets should progress from empirical optimization toward predictive and mechanistic formulation science. Integration of QbD with AI and ML can help predict complex relationships between formulation variables, process conditions, tablet properties and drug release. Physiologically Based Biopharmaceutic Modeling (PBBM) can link in-vitro dissolution with gastrointestinal physiology and pharmacokinetic performance. Process Analytical Technology (PAT) and continuous manufacturing can support real-time monitoring, improved process control and reduced manufacturing variability. Future research should emphasize the integrated application of these technologies for predictive formulation design, robust manufacturing and optimized drug-release performance.

QbD + DoE + Dissolution Modeling + AI/ML + PBBM + PAT + Continuous Manufacturing

The ultimate objective is to establish predictive relationships across the complete development pathway:

Material Attributes → Process Parameters → Tablet Structure → Dissolution → Pharmacokinetics → Product Performance

13. Conclusion

Metformin hydrochloride 500-mg SR matrix tablets require careful control of formulation composition, polymer properties, manufacturing conditions and drug-release behavior. Due to its high solubility and relatively low permeability, achieving controlled release is challenging. HPMC-based hydrophilic matrices regulate drug release through hydration, swelling, gel formation, diffusion, polymer relaxation and erosion. Comprehensive evaluation of precompression properties, tablet characteristics, assay, content uniformity, FTIR, DSC, XRD, swelling, dissolution, release kinetics and stability is essential. The QbD approach integrates QTPP, CQAs, CMAs, CPPs, risk assessment, DoE, optimization, design space and control strategy. Future integration of AI/ML, PBBM, PAT and continuous manufacturing may further improve prediction, process control, consistency and lifecycle management.

Abbreviation

AI : Artificial Intelligence

ANN : Artificial Neural Network

API : Active Pharmaceutical Ingredient

BBD ; Box–Behnken Design

BCS : Biopharmaceutics Classification System

CCD : Central Composite Design

CMA : Critical Material Attribute

CPP : Critical Process Parameter

CQA : Critical Quality Attribute

DoE : Design of Experiments

DSC : Differential Scanning Calorimetry

f_1 : Difference Factor

f_2 : Similarity Factor

FTIR : Fourier-Transform Infrared Spectroscopy

HPMC : Hydroxypropyl Methylcellulose

ICH : International Council for Harmonisation

ML : Machine Learning

PAT : Process Analytical Technology

PBBM : Physiologically Based Biopharmaceutic Modeling

PVP : Polyvinylpyrrolidone

QbD : Quality by Design

QTPP : Quality Target Product Profile

RSM : Response Surface Methodology

SR : Sustained Release

T_{50}% : Time to 50% Drug Release

XRD : X-Ray Diffraction

Declaration:

Ethics approval and consent to participate:

Ethical approval and informed consent were not required for this study, as the manuscript is a literature-based narrative review and involved no original research with human participants or animal subjects.

Clinical Trial No:

As this manuscript is based solely on a narrative review of previously published literature and involves no clinical trials, clinical trial registration was not applicable.

Consent for publication: Clinical trial registration was not applicable, as this manuscript is a narrative review based exclusively on previously published literature and does not involve any clinical trial.

Availability of data and material: Data availability was not applicable, as this manuscript is a narrative review based on previously published literature and does not involve the generation or analysis of original datasets.

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Ruchi Gupta: Writing-review & editing

Niharika sahu: Visualization, schematic design, graphical abstract development and figure illustration.

Rahul Dev: Manuscript writing, review & editing and critical revision.

Rupesh sahu: Literature review, data collection and curation, validation and manuscript evaluation.

Dharmendra sahu: Concept development, methodology and critical review of the manuscript.

Shiv Kumar Bhardwaj: Writing, methodology, visualization and final manuscript editing.

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