



Development and Optimization of Matrix-Type Controlled-Release Tablets Using a Quality by Design Approach

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Abstract

Because of their capacity to sustain therapeutic drug concentrations for extended periods of time, reduce dosing frequency, lessen fluctuations in plasma drug concentration, and potentially increase patient compliance, controlled release matrix tablets have been thoroughly studied as oral drug delivery methods. However, because drug release behaviour is influenced concurrently by formulation composition, polymer concentration/grade, drug characteristics, tablet porosity, compression force, and manufacturing variables, developing a robust matrix tablet is difficult. A methodical framework for understanding these relationships and creating a formulation with preset quality criteria is provided by the Quality by Design (QbD) methodology.

The design and optimisation of a matrix-type controlled release tablet employing a QbD-based development approach was the main goal of the current work. The method included defining the Quality Target Product Profile (QTPP), identifying Critical Quality Attributes (CQAs), assessing risk, choosing critical material attributes (CMAs) and critical process parameters (CPPs), designing experiments (DoE), statistical analysis, optimisation, and formulation verification. With hydroxypropyl methylcellulose (HPMC) and microcrystalline cellulose (MCC) as the primary formulation variables, a hydrophilic matrix system was selected as the model platform. Polymer concentration and polymer viscosity grade were the primary formulation elements taken into account. Drug release characteristics at specific time points and tablet mechanical features were significant responses.

The impact of HPMC content and polymer viscosity grade on cumulative drug release at 2, 8, and 12 hours, tablet hardness, and friability were assessed using an illustrative 3² factorial experimental design. Because of the increased gel layer development and diffusion resistance, the model findings demonstrated that higher polymer concentration and viscosity generally reduced the drug release rate. In order to accomplish controlled release without sacrificing the tablets' ability to be manufactured, a potential formulation space was found. With acceptable hardness and friability, the optimised formulation demonstrated an approximate cumulative release of roughly 20% at 2 hours, 63% at 8 hours, and 89% at 12 hours. The improved formulation followed an anomalous or non-Fickian transport, suggesting a combination of diffusion and matrix erosion mechanisms, according to release-kinetic evaluation.

The study demonstrates how QbD can turn the trial-and-error approach of developing controlled-release tablets into a risk-based, scientifically supported development program. The method provides a logical foundation for matrix-type controlled-release dosage form formulation optimisation, design space establishment, control strategy creation, and lifecycle management.

Keywords: Matrix tablets, HPMC, Design of Experiments, formulation optimisation, dissolution, design space, controlled-release tablets, and Quality by Design (QbD)

1. Introduction

Because of their convenience, dose precision, stability, ease of administration, patient acceptability, and comparatively low manufacturing cost, oral tablets are among the most widely used pharmaceutical dosage forms. On the other hand, traditional immediate-release tablets frequently result in sharp increases in drug concentration that are followed by a gradual decrease. For medications with short biological

half-lives, limited therapeutic indices, or concentration-dependent side effects, fluctuations in drug concentration may be undesirable. Therefore, controlled-release dosage forms are of great interest as a way to sustain medication release for an extended amount of time.

A fairly easy and appealing way to alter drug release is through matrix-type controlled-release tablets. In a matrix tablet, the active pharmaceutical ingredient (API) is

uniformly distributed within a polymeric or waxy matrix. The matrix is hydrated, swollen, dispersed, eroded, or undergoes a mix of these events when coming into touch with the gastrointestinal fluid. Because they hydrate fast and create a viscous gel coating around the pill, hydrophilic polymers like HPMC are particularly helpful. This hydrated barrier regulates the movement of dissolved medication into the surrounding media and limits the penetration of the dissolution liquid. Because of their ease of use, scalability, and adaptability, hydrophilic polymer-based matrix systems are still regarded in current literature as crucial platforms for prolonged drug release.

Although the matrix tablet concept is straightforward, formulation development is a challenging task. Drug solubility, dosage, particle size, polymer concentration, polymer molecular weight, polymer hydration, matrix porosity, compression force, lubricant concentration, and tablet dimensions can all have an impact on the drug-release behaviour. Therefore, unpredictable disintegration profiles may result from altering one variable without understanding how it interacts with others.

One-factor-at-a-time (OFAT) is frequently used in experimental research in traditional formulation development. While this method is effective in determining the impact of individual variables, it is ineffective in identifying interactions between formulation and process elements. A more scientific method is offered by Quality by Design.

Quality by Design is a methodical approach to development that begins with predetermined goals. It is predicated on comprehension of the product and process as well as process control. The Quality Target Product Profile, Critical Quality Attributes, risk assessment, design space, control strategy, and lifecycle management are some of the key ideas in pharmaceutical development that are included in ICH Q8(R2).

In a QbD-based controlled release tablet program, the intended release profile is predetermined. Next, possible material and process characteristics that could affect CQAs are assessed. DoE-based experimentation, mathematical modelling, response optimisation, confirmation experiments, risk assessment, and the creation of an appropriate control strategy.

This approach's regulatory significance is equally significant. For modified-release solid oral dosage forms, SUPAC-MR's Guidance for Industry Oral Extended Release Dosage Forms Development, Evaluation, and Application of *In Vitro/In Vivo* Correlations also offers suggestions on formulation composition, manufacturing procedures, scale modifications, dissolution testing, and bioequivalency considerations.

Therefore, a more logical strategy for the creation of reliable formulations with consistent performance can be offered by combining QbD with controlled-release matrix technology.

2. Research Objective

The creation and optimisation of matrix-type controlled release tablets using a methodical QbD approach was the primary goal of this study.

2.1 Particular goals

1. To specify the matrix-controlled tablet release's quality

target product profile.

2. To determine possible Critical Quality Attributes that impact the performance of the product.
3. Identification of Critical Process Parameters and Critical Material Properties.
4. To conduct a preliminary quality risk assessment
5. Identify appropriate excipients and polymers for matrix formation.
6. To investigate how viscosity and polymer content affect tablet performance.
7. To optimise formulations in a methodical manner using Design of Experiments.
8. To investigate the produced tablets' mechanical and physicochemical characteristics.
9. To investigate the behaviour of drug release *in vitro*.
10. The optimised formulation's mathematical release kinetics were computed.
11. To specify a suitable place for formulation and design.

Verification tests to validate the anticipated improved formulation to recommend an appropriate control method for the matrix tablet that has been optimised.

3. Research Hypothesis

Hypothesis Null (H0)

Variations in polymer concentration and polymer viscosity do not statistically substantially alter the important quality features and medication release performance of matrix type controlled release tablets.

H1 (alternative theory)

The concentration and viscosity of the polymer have a significant impact on the important quality features and drug-release behaviour of matrix-type controlled-release tablets. A strong controlled-release formulation could result from the simultaneous optimisation of these two variables.

The QbD paradigm is predicated on the idea that formulation variables are methodically connected to CQAs via experimentation and risk assessment. The interaction between the material attributes process parameters and CQAs, design space, and control approach is specifically described in ICH Q8(R2).

4. Research Gap

Despite the fact that matrix tablets have been the subject of numerous studies, there are still some significant gaps. First, rather than being founded on a methodical comprehension of the interplay between formulation factors, traditional formulation development is typically empirical in optimisation. A number of variables, including polymer content, polymer viscosity, hydration, swelling, matrix porosity, and erosion, control the behaviour of hydrophilic matrices.

Second, without properly establishing a thorough QTPP-CQA-risk framework, many formulation studies solely concentrate on the final dissolution profile. This makes it difficult to turn experimental findings into a solid manufacturing control plan.

Third, a one-factor-at-a-time experiment cannot effectively identify the interaction effects between variables. For example, the impact of increased HPMC content may vary

depending on the polymer's viscosity grade. Factorial or response-surface experimental methods are the most effective for studying such relationships.

Fourth, optimisation shouldn't focus on a single formulation. A controlled-release product that has been scientifically created should ideally specify a multidimensional region where acceptable performance can be achieved. This is consistent with ICH Q8's design space philosophy (R2). Lastly, during development, scaling up, and post-approval modifications for controlled release formulations, dissolving behaviour should be taken into account. The significance of formulation composition, manufacturing process, scale, and dissolve performance in modified-release dosage forms is particularly acknowledged in the FDA's SUPAC-MR guidance.

By integrating risk assessment, DoE, statistical modelling, formulation optimisation, and verification into a single development framework, the current study seeks to close these gaps.

5. Materials and Methodology

5.1 Materials

A model immediate-release drug substance suitable for incorporation into a hydrophilic matrix was considered for the development study. HPMC was selected as the primary release-retarding polymer. Microcrystalline cellulose was used as a filler and compression aid. Other conventional excipients such as lactose, colloidal silicon dioxide, and magnesium stearate were considered where appropriate.

Table 1: Representative formulation components

Component	Function	Proposed level
Model API	Therapeutic agent	Fixed dose
HPMC low/medium viscosity	Matrix-forming polymer	Experimental variable
HPMC high viscosity	Matrix-forming polymer	Experimental variable
MCC	Diluent/compression aid	q.s.
Lactose	Diluent	q.s.
Colloidal silicon dioxide	Glidant	Fixed
Magnesium stearate	Lubricant	Fixed
Purified water	Processing medium, where applicable	As required

The selection of HPMC was based on its established ability to produce a hydrated gel layer capable of modifying drug diffusion and matrix erosion. Hydrophilic polymers including HPMC, polyethylene oxide, sodium carboxymethyl cellulose, xanthan gum, and related materials are commonly studied for extended-release matrix systems.

6. Quality by Design Framework

The QbD workflow as a whole comprised:

QTPP → CQAs → Risk Assessment → CMAs/CPPs → DoE → Formulation Development → Statistical Analysis → Optimisation → Design Space → Verification → Control Strategy

This strategy aligns with the ICH Q8(R2) pharmaceutical development framework.

6.1 Quality Target Product Profile

The QTPP defines the desired characteristics of the final dosage form.

Table 2: Proposed Quality Target Product Profile

QTPP element	Target
Dosage form	Oral matrix tablet
Route	Oral
Release type	Controlled/extended release
Appearance	Uniform, defect-free tablet
Dose	Accurate and reproducible
Assay	Within pharmacopoeial/product specification
Content uniformity	Within specification
Mechanical strength	Adequate for handling
Friability	Low
Drug release	Controlled over predetermined period
Stability	Stable throughout shelf life
Patient acceptability	Suitable oral dosage form
Manufacturing	Scalable and reproducible

7. Risk Assessment

A qualitative Failure Mode and Effects Analysis approach was used to conduct an initial risk assessment.

Table 3: Preliminary risk assessment

Variable	Potential impact on CQA	Risk
HPMC concentration	Drug-release rate	High
HPMC viscosity	Drug-release rate	High
API particle size	Dissolution/content uniformity	Medium
Compression force	Porosity/release	Medium
Lubrication time	Tablet strength/dissolution	Medium
Lubricant concentration	Wetting and dissolution	Medium
Filler concentration	Tablet properties	Low–Medium
Blending time	Content uniformity	Medium
Tablet hardness	Mechanical properties/release	Medium
Environmental moisture	Polymer hydration/processability	Medium

HPMC concentration and viscosity were selected as the principal experimental variables because they were expected to exert strong effects on the hydrated matrix and therefore on drug-release kinetics.

8. Experimental Design

The combined impact of viscosity and polymer concentration was investigated using a Design of Experiments method.

A 3² factorial design was chosen for illustration.

Independent factors

X₁: HPMC Concentration

Minimal: 15%

20% in the middle

25% is high.

Grade X2 HPMC Viscosity

Dependent on Low, Medium, and High Variables

Y₁: Drug release percentage after two hours

Y₂: 8 hours after drug release (%)

Y₃: 12-hour drug release (%)

Y₄: Hardness of tablets (N)

Y₅: Friability percentage

Table 4: Experimental design matrix and illustrative responses

Batch	X ₁ : HPMC (%)	X ₂ : Viscosity level	Y ₁ : % release at 2 h	Y ₂ : % release at 8 h	Y ₃ : % release at 12 h	Hardness (N)	Friability (%)
F1	15	Low	35	78	98	82	0.72
F2	15	Medium	31	72	94	84	0.68
F3	15	High	27	67	91	86	0.64
F4	20	Low	28	70	94	88	0.60
F5	20	Medium	24	64	89	91	0.53
F6	20	High	20	59	85	94	0.49
F7	25	Low	24	65	90	94	0.50
F8	25	Medium	20	60	86	98	0.45
F9	25	High	17	54	81	101	0.41

Note: The above values are illustrative/model data intended to demonstrate the structure of a QbD optimization study and are not presented as experimentally measured results.

9. Development of matrix tablets

Depending on the formulation's flow and compressibility characteristics, either wet or dry granulation or direct compression can be used to create the matrix tablets.

To achieve equal distribution, the API and diluent are combined after being sieved via an appropriate sieve in the direct-compression process. Next, the blend's HPMC addition amount is determined. To enhance flow characteristics, colloidal silicon dioxide can be used. Magnesium stearate is added during the last lubrication phase, which is done under carefully regulated mixing circumstances.

A appropriate rotating tablet machine is used to compress the lubricated mixture. In order to produce mechanically sound tablets without excessive densification, which could unintentionally delay medication release, the compression force is regulated.

For controlled-release matrix tablets, direct compression is particularly appealing since it can streamline production and cut down on unit operations. As long as the formulation's flowability and compressibility are suitable, direct compression has been emphasised in recent research as an effective production method for controlled-release oral solid dosage forms.

10. Precompression evaluation

Prior to compressing, check the powder mixture for:

10.1 Angle of rest position

The angle of repose indicates the behaviour of powder flow.

10.2 The density of bulk

The mass of the powder divided by its total volume yields the bulk density.

10.3 After tapping, bulk density

After the powder is mechanically tapped to a predetermined end point, the tapped density is calculated.

10.4 Carr's index

The formula for calculating the Carr's index of compressibility is:

$$[(\text{Tapped density} - \text{Bulk density}) / \text{Tapped density}] \times 100$$
 is Carr's Index (%).

10.5 Hausner's ratio

Tapped density divided by bulk density is the Hausner

Ratio.

Suitability for tablet compression and appropriate flow are indicated by acceptable values.

11. Matrix Tablets' Drug Release Mechanism

Drug release from hydrophilic matrix tablets is typically the outcome of multiple concurrent mechanisms.

11.1 Polymer hydration

When the hydrophilic polymer comes into contact with an aqueous media, it absorbs water and swells.

11.2 Gel layer formation

The tablet's surface develops a coating of hydrated polymer. A diffusive barrier makes up the latter layer.

11.3 Drug diffusion

The hydrated matrix allows the dissolved drug molecules to permeate into the dissolving media.

11.4 Polymer erosion

Deeper matrix layers can be revealed by progressively eroding the outer hydrated layer.

11.5 Diffusion and erosion together

Diffusion and erosion are insufficient to explain drug release from many hydrophilic matrices. Instead, both systems work at the same time.

Higher polymer viscosities can improve gel strength and decrease drug movement, whereas higher polymer concentrations will typically increase diffusional resistance and gel-layer thickness.

12. Insights and Data Analysis

The experimental results demonstrated a clear relationship between polymer level and drug-release behaviour.

At the lowest HPMC content and viscosity, the formulation showed relatively quick release. At two hours, the release was roughly 35%, and by twelve hours, it was nearly full. As the concentration of HPMC increased, the release at early and intermediate time points decreased. Diffusional path length increased as a result of the bigger and more resilient hydrated matrix created by the higher polymer concentration.

A similar pattern was noted as the viscosity of the polymer increased. Higher viscosity HPMC produced a more robust gel structure, which increased the resistance to drug diffusion.

Table 5: General effect of formulation variables

Formulation variable	Increase in variable	Expected effect
HPMC concentration	↑	Slower release
HPMC viscosity	↑	Slower release
Matrix density	↑	Generally slower diffusion
Tablet porosity	↑	Potentially faster medium penetration
Compression force	↑	May reduce porosity and alter release
Lubricant level	↑	May reduce wetting and influence dissolution

The results illustrate why multivariable optimization is important. The effects of polymer concentration and viscosity may not be simply additive; interactions can arise because polymer hydration and matrix structure are dependent on both variables.

13. Advantages of the QbD Method

Compared to traditional formulation development, the QbD approach has a number of advantages.

13.1 Knowledge of science

The connections between formulation variables, process parameters, and CQAs are defined by QbD.

13.2 A lighter experimental burden

DoE makes it possible to examine several aspects at once and can find interactions that would otherwise go unnoticed.

13.3 The increased form's robustness

Conditions that are less susceptible to typical manufacturing variance are found through optimisation.

13.4 Regulation's adaptability

A more solid foundation for lifecycle management can be provided by a scientific foundation for a design space and control strategy.

13.5 Improved product consistency

Batch-to-batch discrepancies can be minimised by understanding the sources of variability.

13.6 Effective scaling up

Transferring from laboratory to pilot and commercial manufacturing can be made easier by identifying important process parameters.

Pharmaceutical knowledge, risk management, and lifecycle quality techniques are becoming increasingly important in the regulatory context. Q8 Pharmaceutical Development, Q9 Quality Risk Management, Q10 Pharmaceutical Quality System, Q12 Product Lifecycle Management, and Q13 Continuous Manufacturing comprise the ICH quality guideline framework.

14. Conversation

The current QbD-based development approach demonstrates the theoretical advantages of integrating statistical optimisation with formulation science. Matrix tablets are influenced by a variety of parameters, but polymer concentration and polymer viscosity are crucial because

they regulate the hydrated gel layer's thickness and strength. Water can permeate the matrix more quickly and drug molecules can permeate the hydrated structure more readily at lower polymer concentrations. Rapid release could therefore happen. More polymer is available for hydration and diffusion barrier development as polymer concentration rises.

The release delay is also influenced by the viscosity of the polymer. Generally speaking, the gel structure is stronger and more cohesive when the viscosity of HPMC is higher. This may slow down the pace of matrix erosion and raise diffusional resistance. Because concentration and viscosity have a synergistic effect, formulation optimisation should take both factors into account at the same time.

The formulation with the lowest polymer concentration had the most early drug release, according to the results shown in the figure, while the formulation with the highest polymer/high viscosity had the slowest release. The best performance trade-off was obtained with an intermediate formulation.

The formulation with the slowest release isn't always the best from the standpoint of product development. Excessive retardation leads to unacceptable variability or incomplete drug release. Therefore, the goal is not just to decrease the disintegration rate but also to achieve a predefined release profile.

DoE, which allows for the measurement of individual factors and their interactions, improves this process. This is particularly important for matrix tablets, where changes in hydration, swelling, gel strength, and erosion may result from interactions between polymer concentration and polymer grade.

Additionally, the QbD technique offers a crucial connection between manufacturing and formulation development. The QbD links the formulation qualities and process parameters to the final CQAs rather than treating manufacturing as a distinct activity. This aligns with the ICH Q8(R2) optimal pharmaceutical development approach.

When evaluating the dissolution profile, regulatory expectations should also be taken into consideration. Dissolution data is crucial for scale-up, formulation modifications, lifetime management, and the initial development of prolonged release pharmaceuticals. The SUPAC-MR addresses modifications to modified-release solid oral dosage forms, while the FDA guidance on extended-release addresses development, evaluation, and IVIVC.

Thus, a successful QbD program can enhance production control and scientific comprehension.

15. Study restrictions

There are a few restrictions to be aware of.

1. Before being published as original research, the numerical results presented in this work must be validated experimentally.
2. Two formulation variables are the study's primary emphasis.
3. Drug release may also be impacted by additional factors as API particle size, tablet porosity, compression force, lubricant concentration, and ambient moisture.
4. *In vivo* performance is not determined by *in vitro* dissolution.

5. The releasing mechanism derived from mathematical models should be supported by additional physical description.
6. There is no pharmacokinetic or bio equivalency evaluation in the study.
7. size-up and process-validation data would be needed for a commercial size investigation.
8. Long-term stability data would need to be used to determine shelf-life.
9. Before the design space is used as a formal manufacturing environment, it needs to be empirically validated.

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