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# Development of Optimal Extended-Release Formulations for Poorly Water-Soluble Drug (Mefenamic Acid) Using Quality by Design Principles

Samya M Khaled [1*]

1. Faculty of Pharmacy, Elmergib University, Alkhmos, Libya

## ABSTRACT

The aim of this project was to develop optimal extended-release tablets of mefenamic acid using the principles of Quality by Design (QbD). Mefenamic acid is a poorly water-soluble drug, classified as a BCS Class II drug (low solubility, high permeability). The formulations were designed using the Design of Experiment (DoE) feature of JMP software. Lactose, in the range of 15–25%, was used as a filler, while HPMC K100M, in the range of 10–15%, was used as a modified-release agent to design 12 different formulations. Various physical parameters of the tablets, namely thickness, diameter, hardness, friability, and in vitro release, were evaluated. The physical parameters of the compressed tablets were found to be satisfactory for all formulations. In vitro drug release studies were performed in 900 mL of phosphate buffer medium at pH 7.1 containing 2% cetyltrimethyl ammonium bromide (CTAB) using a dissolution apparatus (paddle method). The in vitro release profiles indicated that all formulations of mefenamic acid functioned effectively as extended-release tablets. The drug release percentage of all formulations met the Quality Target Product Profile (QTPP) goal of achieving 50–85% drug release within six hours.

**KEYWORDS:** Mefenamic acid, Extended-release tablets, Quality by Design (QbD), Poorly water-soluble drugs, BCS Class II drugs, Hydrophilic matrix tablets

*Corresponding author: : samyia198576@yahoo.com*

## INTRODUCTION

During the last few decades, the popularity of poorly water-soluble drugs has been increasing due to various discoveries. However, these drugs have several shortcomings, such as low dissolution rate, low permeability, limited absorption, and insufficient and variable bioavailability (Leuner and Dressman, 2000). In addition, more than 90% of new chemical entities (NCEs) are classified as poorly water-soluble compounds. According to the Biopharmaceutics Classification System (BCS), Class I drugs have high permeability and high solubility, Class II drugs have high permeability and low solubility, Class III drugs have high solubility and low permeability, and Class IV drugs have low permeability and low solubility (Benet, 2013). According to Benet (2014), BCS Class II drugs often show limited oral bioavailability and saturation of exposure at high doses. The solubility of the drug, the dissolution rate, and permeability are important parameters for orally administered drugs due to their direct effect on drug absorption (Kerns and Di, 2008). Furthermore, poorly water-soluble drugs (BCS Class II) often have short biological half-lives, which necessitates frequent administration throughout the day (Wan et al., 2011; 2012). This leads to considerably fluctuating drug concentrations in plasma and potential drug toxicity (Huang et al., 2006). Therefore, there is a need for the design and development of an extended-release oral dosage form instead of the conventional dosage form to improve the drug's therapeutic levels and safety, reduce side effects, and increase patient compliance. The optimal formulation for improving the bioavailability and dissolution of poorly water-soluble BCS Class II drugs, such as mefenamic acid, with short biological half-lives would enhance their solubility and control their release.

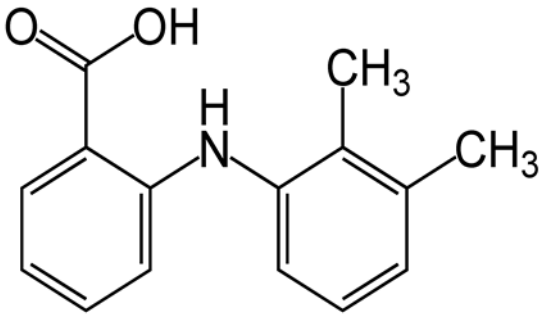


**Figure 1.** Chemical structure of mefenamic acid

In this study, mefenamic acid extended-release tablets containing different concentrations of polymer (HPMC K100M) and channeling agent (lactose) were designed and developed using Quality by Design (QbD) principles for solubility improvement, controlled release, and oral bioavailability enhancement of mefenamic acid, given its short half-life. The *in vitro* release of mefenamic acid from the tablets was evaluated using the paddle method (Erweka DT6, Germany)

### Materials and Methods

The methods included selection of dissolution medium, selection of dissolution apparatus, and grinding and mixing processes.

### Selection of Dissolution Medium

The dissolution medium and its conditions should mimic physiological conditions as closely as possible (Brittain, 2006). The choice of dissolution medium for dissolution testing depends upon the drug solubility, the purpose of the dissolution testing, and practical and economic considerations (Jorgensen and Bhagwat, 1998). The dissolution medium usually consists of water or buffer solutions (Brittain, 2006). Testing is commonly performed at 37°C ± 0.5°C (Hühn and Langguth, 2013). Surfactants can be used in a dissolution medium to enhance the solubility of poorly water-soluble drugs. It has been found that using a surfactant for the dissolution test provides good *in vivo*/*in vitro* correlation (Hühn and Langguth, 2013). To reach sink conditions, a small amount of surfactant should be added to the dissolution medium (Peter et al., 2014). However, using too much surfactant within the dissolution medium leads to accelerated percentage release of poorly water-soluble drugs from HPMC matrix tablets, as well as an increased erosion process of the HPMC matrix (Peter et al., 2014).

### Selection of Dissolution Apparatus

USP Apparatus I (basket type) is not suitable for extended-release formulations because the matrix could clog the holes in the basket and disrupt the hydrodynamics of the dissolution test (Jorgensen and Bhagwat, 1998). The type of dosage form determines the selection of the dissolution apparatus used for the development and validation method (Chan, 2003; 2004). Commonly, dissolution testing for immediate-release formulations is performed using Apparatus 1 (basket method) and Apparatus 2 (paddle method) (Aulton and Taylor, 2013). Apparatus 3 (reciprocating cylinder) is commonly used for testing extended-release formulations and dosage forms that require release profiles at different pH values and more sampling time points (Anand et al., 2011).

### Mixing and Grinding Processes

Proper mixing is a critical factor that may influence the drug release percentage of tablets (Remington and Hendrickson, 2006). If the mixing process with lubricant is insufficient, the lubricant could be inadequately distributed, leading to variation in tablet hardness and tablet dissolution (Zheng,

2008; 2009). However, the mixing time should be short, as prolonged mixing leads to an increase in the negative impacts of hydrophobic lubricant (Zheng, 2008; 2009). The grinding process is used to increase the percentage of drug release of poorly water-soluble drugs (Remington and Hendrickson, 2006). The coarse materials should be ground to a 10-to-20-micron range (Felton and Remington, 2013).

## Control Strategy for Mefenamic Acid Extended-Release Tablets

Table 1 shows the control strategy for the design and development of the mefenamic acid extended-release tablets to maintain the attributes of the tablets within the required ranges. The control space is used to show the upper and/or lower range for the critical formulation variables and critical process parameters (CPPs), which should be routinely controlled during manufacture to ensure reproducibility (Basalious et al., 2011). In addition, the control space should be within the design space (Basalious et al., 2011). When the control space is much smaller than the design space, it results in more robust processes and products (Sangshetti et al., 2013).

Formulation understanding developed around mefenamic acid extended-release tablets demonstrates that the polymer percentage, channeling agent percentage, and lubricant are the critical factors that determine the quality of the final product. In addition, the mixing process is critical during the manufacturing of mefenamic acid formulations.

| Attributes | Control Strategy |
|---|---|
| Polymer | HPMC Polymer Grade K100M Percentage used: 12.5% of the total weight of the tablet |
| Channeling agent | Lactose Percentage used: 20% of total weight of the tablet |
| Lubricant | Magnesium stearate 1.5–2% of the total weight of the formulation |
| Mixing | Thorough mixing of ingredients Time of mixing: 10 minutes Time of mixing with lubricant: 10 minutes Mixed in a small polyethylene bag |
| Dissolution test | Apparatus 2 – Erweka DT6 paddle Dissolution medium – 900 mL of phosphate buffer at pH 7.1 with 2% CTAB Maintained temperature: 37°C Rotation speed: 100 rpm 5 mL samples removed at 1, 2, 3, 4, 5, and 6 hours and replaced with 5 mL of fresh solvent Measurement on UV spectrophotometer at 285 nm |

**Table 1.** Control strategy for the design and development of mefenamic acid extended-release tablets

## Preparation of Mefenamic Acid Extended-Release Tablets

The mefenamic acid extended-release tablets were prepared by the direct compression method. The mefenamic acid, polymer, lactose, and microcrystalline cellulose were weighed separately and mixed thoroughly for 10 minutes in a small polyethylene bag using the tumbling action. Finally, 2% magnesium stearate was added, and the mixture was mixed again for 10 minutes to ensure even coating of the particle surface by the lubricant. The tablets were prepared using a single punch tablet machine (Carver, INC., USA).

## Design of Experiment (DoE)

An experimental design with two factors and three levels with 12 runs was developed to observe the influence of significant formulation factors on the release of mefenamic acid using a custom design (JMP statistical software). Furthermore, the DoE was used to understand the inter-relationships between the factors and to optimize the levels of factors. The two factors were the percentage of polymer (HPMC K100M), ranging from 10% to 15%, and the percentage of the channeling agent (lactose), ranging from 15% to 25%. Tables 2 and 3 show the composition of the formulations prepared.

**Table 2.** Percentage composition of mefenamic acid extended-release tablets (100 mg)

| Ingredients (mg/tablet) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Mefenamic acid | 30 | 30 | 30 | 30 | 30 | 30 |
| HPMC K100M | 12.5 | 15 | 15 | 10 | 12.5 | 12.5 |
| Lactose | 20 | 25 | 20 | 20 | 25 | 20 |
| Microcrystalline cellulose | 35.5 | 28 | 33 | 38 | 30.5 | 35.5 |
| Magnesium stearate | 2 | 2 | 2 | 2 | 2 | 2 |
| Total tablet weight (%) | 100 | 100 | 100 | 100 | 100 | 100 |

**Table 3.** Percentage composition of mefenamic acid extended-release tablets (100 mg)

| Ingredients (mg/tablet) | F7 | F8 | F9 | F10 | F11 | F12 |
|---|---|---|---|---|---|---|
| Mefenamic acid | 30 | 30 | 30 | 30 | 30 | 30 |
| HPMC K100M | 10 | 12.5 | 15 | 12.5 | 10 | 12.5 |
| Lactose | 25 | 15 | 15 | 20 | 15 | 20 |
| Microcrystalline cellulose | 33 | 40.5 | 38 | 35.5 | 43 | 35.5 |
| Magnesium stearate | 2 | 2 | 2 | 2 | 2 | 2 |
| Total tablet weight (%) | 100 | 100 | 1000 | 100 | 1000 | 100 |

## Evaluation of Mefenamic Acid Tablets

Several physical parameters of the mefenamic acid extended-release tablets were evaluated. The thickness, diameter, hardness, and friability were measured using the thickness/hardness tester (Erweka Apparatus, Germany) and friability tester (Pharma Apparatus, Germany). The thickness/hardness tester and friability tester are illustrated in Figures 2 and 3.

**Figure 2.** Hardness/thickness tester (Pharma Apparatus, Germany).


**Figure 3.** Friability tester (Pharma Apparatus, Germany).

## Calibration Curve of Mefenamic Acid Standard Solution

A stock standard solution equivalent to 1 mg/mL mefenamic acid was prepared by dissolving 30 mg of pure drug in pH 7.1 phosphate buffer containing 2% CTAB, and the volume was made up to 100 mL in a calibrated flask.

Different aliquots (0.5, 1.0, 2.0, and 3.0 mL) of the 1 mg/mL mefenamic acid stock solution were accurately measured and transferred into a series of 100 mL volumetric flasks, and the volume was adjusted to the mark with pH 7.1 phosphate buffer containing 2% CTAB. The absorbance of these dilutions was then measured using a UV spectrophotometer at a wavelength of 285 nm.

**Table 4.** Concentration and absorbance from the calibration curve of mefenamic acid

| Concentration (mg/100 mL) | Absorbance (nm) |
|---|---|
| 0.005 | 0.342 |
| 0.01 | 0.552 |
| 0.02 | 1.077 |
| 0.03 | 1.561 |

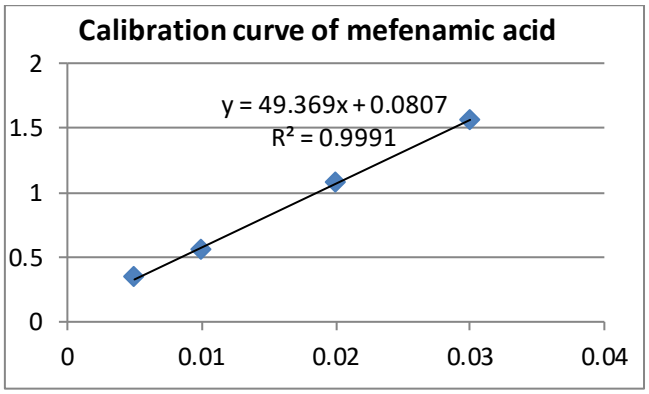


**Figure 4.** Calibration curve of mefenamic acid

## In Vitro Drug Release Studies

The dissolution test apparatus (Erweka DT6, Germany) was used to measure the drug release percentage of the mefenamic acid extended-release tablets using the paddle method with constant rotation at 100 rpm according to USP. The dissolution medium consisted of 900 mL of pH 7.1 phosphate buffer containing 2% CTAB at a temperature of 37°C. One mefenamic acid extended-release tablet was placed in each vessel of the dissolution apparatus. Samples (5 mL) were taken at intervals of 1, 2, 3, 4, 5, and 6 hours and filtered using membrane filters to measure the drug release. Each 5 mL sample removed was replaced with 5 mL of fresh dissolution medium. The mefenamic acid release in each sample was measured using a UV-visible spectrophotometer at a wavelength of 285 nm, and the percentage release was calculated. The dissolution test apparatus (Erweka DT6, Germany) and UV-visible spectrophotometer (Evolution 60S, USA) are shown in Figures 5 and 6.

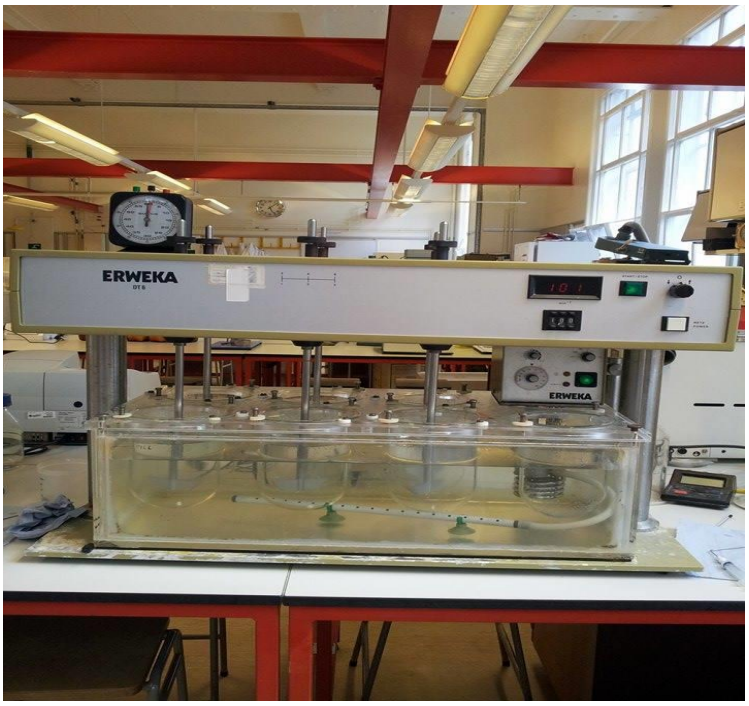


**Figure 5.** Dissolution apparatus (Erweka DT6, Germany).


**Figure 6.** UV-visible Spectrophotometer (Evolution 60S, USA).

## Results and Discussion

In the present study, the DoE principle was applied to systematically evaluate the impact of varying polymer concentrations (HPMC K100M) from 10% to 15% and channeling agent (lactose) concentrations from 15% to 25% on the percentage of drug release. This approach was used to determine the most significant factors affecting the drug release percentage and to establish their optimal levels for optimizing mefenamic acid formulations. The 12 formulations were prepared by varying the percentages of polymer and

filler, always keeping the drug quantity and the total tablet weight constant according to the DoE principle (custom design). Two products with similar properties, i.e., a soluble channeling agent with hydrophilic nature (lactose) and hydrophilic HPMC K100M, were chosen as the matrix-forming materials for preparing the extended-release drug in solid dosage form.

## Physical Evaluation of Mefenamic Acid Extended-Release Tablets

The mefenamic acid formulations were evaluated for physical parameters such as thickness, diameter, hardness, and friability (Table 5). The mean thickness and diameter of the tablets ranged from 2.62 mm to 2.69 mm and 5.89 mm to 5.96 mm, respectively. The hardness of the tablets was found to be in the range of 6.07 kg/cm² to 7.63 kg/cm², with standard deviation less than 2.0%. Siddiqui and Nazzal (2007) considered tablet hardness a major characteristic due to the bonding properties of the filler and the compression force of the compressed ingredients. The friability of all formulations was not more than 0.4%. The friability of mefenamic acid formulations was found to be less than 1%, which is within the standard specification range.

**Table 5.** Physical evaluation of mefenamic acid extended-release tablets (100 mg)

| Formulation Code | Thickness (mm) | | Diameter (mm) | | Hardness (kg/cm²) | | Friability (%) |
|---|---|---|---|---|---|---|---|
| | Mean | STDEV | Mean | STDEV | Mean | STDEV | |
| 1 | 2.66 | 0.032 | 5.96 | 0.0054 | 6.75 | 0.34 | 0.36 |
| 2 | 2.68 | 0.036 | 5.89 | 0.16 | 6.56 | 0.23 | 0.21 |
| 3 | 2.65 | 0.008 | 5.95 | 0.005 | 7.37 | 0.42 | 0.16 |
| 4 | 2.62 | 0.023 | 5.95 | 0.005 | 6.07 | 0.40 | 0.40 |
| 5 | 2.64 | 0.009 | 5.95 | 0.005 | 6.45 | 0.52 | 0.40 |
| 6 | 2.65 | 0.010 | 5.95 | 0.007 | 7.06 | 0.25 | 0.23 |
| 7 | 2.66 | 0.017 | 5.96 | 0.005 | 6.52 | 0.54 | 0.34 |
| 8 | 2.67 | 0.017 | 5.95 | 0.004 | 6.99 | 0.21 | 0.34 |
| 9 | 2.69 | 0.023 | 5.95 | 0.004 | 6.79 | 0.39 | 0.34 |
| 10 | 2.64 | 0.016 | 5.95 | 0.004 | 6.90 | 0.33 | 0.33 |
| 11 | 2.62 | 0.031 | 5.95 | 0.004 | 7.63 | 0.37 | 0.23 |
| 12 | 2.66 | 0.030 | 5.96 | 0.006 | 6.88 | 0.55 | 0.30 |

## In Vitro Drug Release Profiles

The drug release profiles of mefenamic acid from the formulations prepared at different concentrations of HPMC K100M and lactose revealed that the drug release percentage for all formulations was inversely related to the concentration of the polymer. A higher concentration of polymer (HPMC K100M) in the mefenamic acid formulation led to a decrease in the percentage of drug release. A higher polymer concentration had a strong retardant impact on the release of carbamazepine from the tablet matrix (Barakat et al., 2009). In contrast, the lactose concentration slightly influenced the rate of drug release. As seen in Figures 8, 10, and 12, formulations (F4, F7, and F11) containing 10% of the polymer (HPMC K100M) were unable to adequately control the release, with more than 30% of mefenamic acid released in one hour and more than 70% of the drug available in the dissolution medium in six hours. Reza et al. (2003) pointed out that a decrease in HPMC concentration in formulations led to an increase in the release rate of theophylline, diclofenac sodium, and diltiazem hydrochloride from matrix tablets. The decrease in HPMC concentration could cause porosity with a low degree of tortuosity in the hydrated matrix, leading to a reduction in gel strength and fast diffusion of the dissolved drug from the tablet matrix (Skoug et al., 1993).

From Figures 7, 9, 10, 11, and 12, it can be seen that the tablets (F1, F5, F6, F8, F10, and F12) with a polymer concentration of 12.5% had a good extended-release profile, releasing between 15% and 30% of mefenamic acid in the dissolution medium in one hour and about 60% of the drug after six hours. On the other hand, as shown in Figures 7, 8, and 11, the formulations (F2, F3, and F9) containing 15% of the polymer (HPMC K100M) released between 10% and 20% of the drug after the first hour and between 40% and 55% of the drug in six hours. An increase in polymer concentration led to a delayed release of verapamil hydrochloride from the matrix tablet (Baviskar et al., 2013). According to Barakat et al. (2009), a high concentration of HPMC caused a decrease in the release of carbamazepine from the tablet matrix, and the non-Fickian diffusion changed to Case II transport with a high concentration of HPMC in the formulation, exhibiting a considerable contribution via erosion. The propranolol hydrochloride tablet containing a high level of polymer showed incomplete release (Huang et al., 2003).

The percentage release of mefenamic acid significantly decreased in one hour and in six hours when there was an increase in the concentration of HPMC K100M, probably because the hydration of polymer and formation of the gel layer increase the diffusion path length, as well as increasing the resistance to diffusion. According to Kiortsis et al. (2005), the increase in HPMC concentration caused an increase in the thickness of the continuous barrier surrounding the drug particles, which led to a reduction in the diffusion rate of the dissolved drug and thus a decrease in the percentage of drug release.

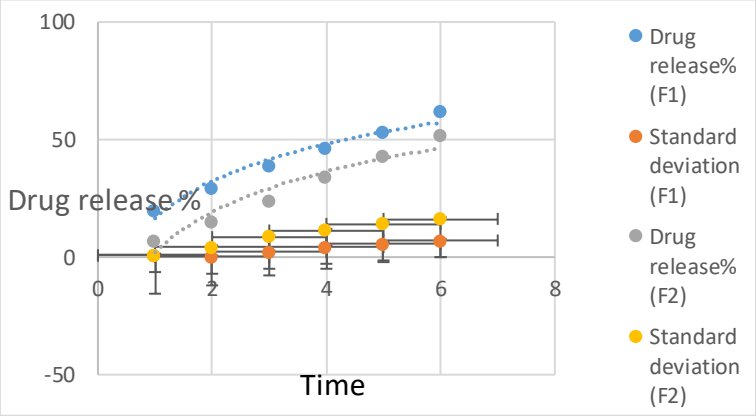


**Figure 7.** Drug release profiles of mefenamic acid formulations in pH 7.1 phosphate buffer containing 2% CTAB over six hours. F1 containing 12.5% HPMC K100M and 20% lactose; F2 containing 15% HPMC K100M and 25% lactose.

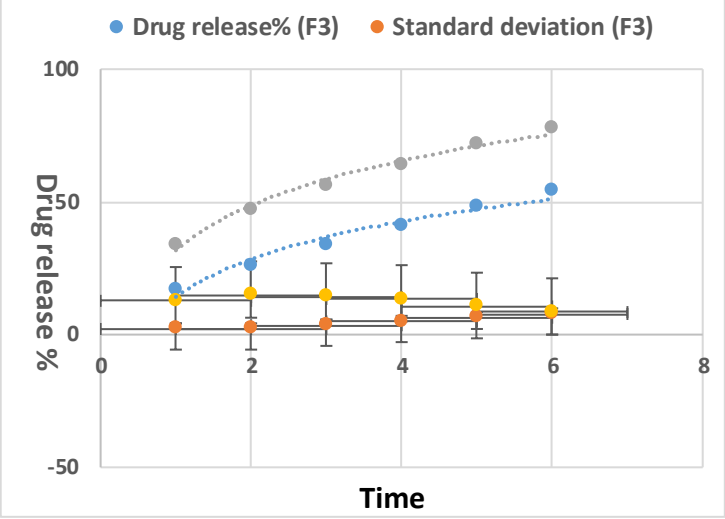


**Figure 8.** Drug release profiles of mefenamic acid formulations in pH 7.1 phosphate buffer containing 2% CTAB over six hours. F3 containing 15% HPMC K100M and 20% lactose; F4 with 10% HPMC K100M and 20% lactose.

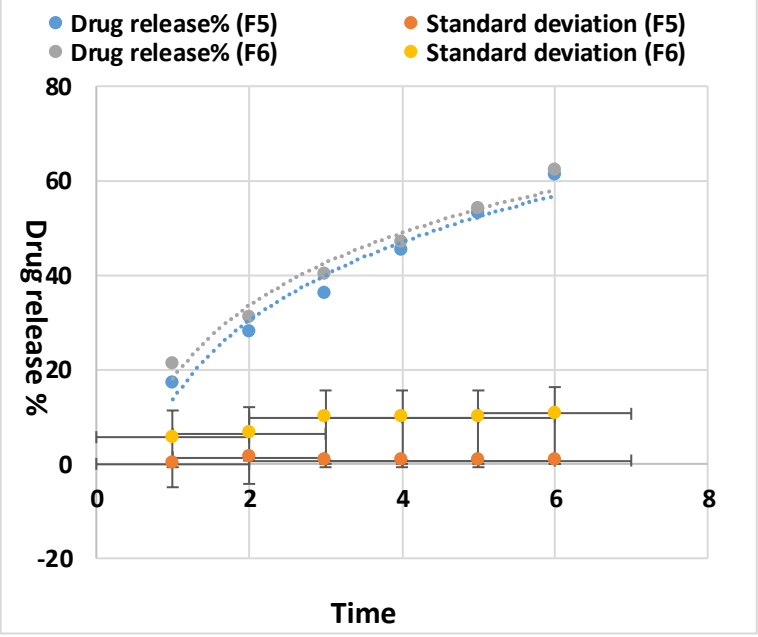


**Figure 9.** Drug release profiles of mefenamic acid formulations in pH 7.1 phosphate buffer containing 2% CTAB over six hours. F5 containing 12.5% HPMC K100M and 25% lactose; F6 with 12.5% HPMC K100M and 20% lactose.

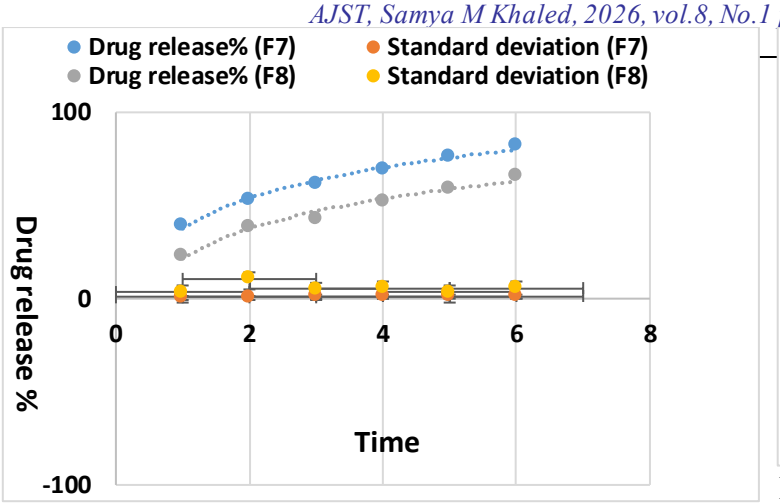


**Figure 10.** Drug release profiles of mefenamic acid formulations in pH 7.1 phosphate buffer containing 2% CTAB over six hours. F7 with 10% HPMC K100M and 25% lactose; F8 containing 12.5% HPMC K100M and 15% lactose.

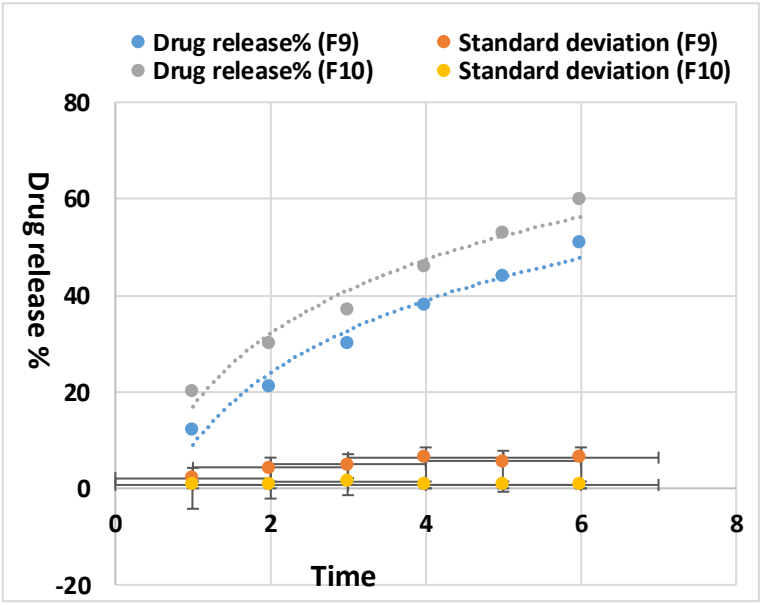


**Figure 11.** Drug release profiles of mefenamic acid formulations in pH 7.1 phosphate buffer containing 2% CTAB over six hours. F9 containing 15% HPMC K100M and 15% lactose; F10 with 12.5% HPMC K100M and 20% lactose.

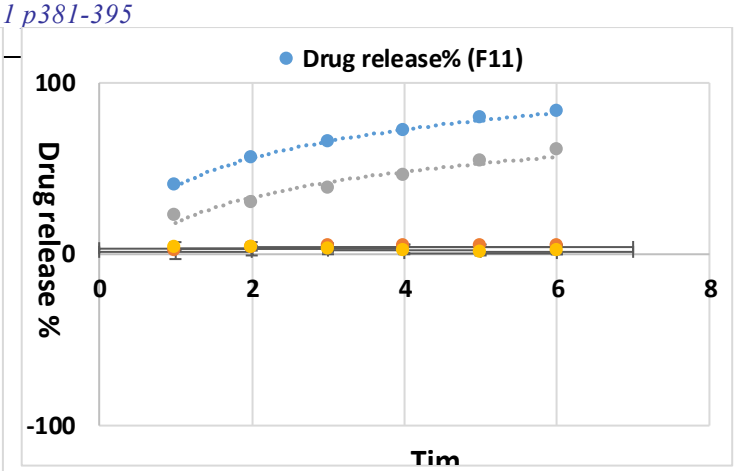


**Figure 12.** Drug release profiles of mefenamic acid formulations in pH 7.1 phosphate buffer containing 2% CTAB over six hours. F11 with 10% HPMC K100M and 15% lactose; F12 containing 12.5% HPMC K100M and 20% lactose.

## Prediction Profiler of Drug Release Percentage

Figure 13 shows a prediction profiler revealing the drug release percentage of mefenamic acid extended-release tablets after the first hour. This figure shows that HPMC K100M concentration has a greater effect on the drug release percentage compared to the lactose concentration, as indicated by the steeper slope for HPMC K100M and the less steep slope for lactose concentration. Lactose is widely used as a channeling agent for tablet formulations (Husen et al., 2012). It is a water-soluble channeling agent and can modify the drug release, thus producing faster release profiles due to its channeling effect (Husen et al., 2012). The value of desirability for the drug release percentage and the two factors after the first hour was approximately 0.824. It is important to clarify the suitable desirability functions for response and factors through optimization (Kaul et al., 2011). The value of desirability ranges from 0 to 1 (Kaul et al., 2011).

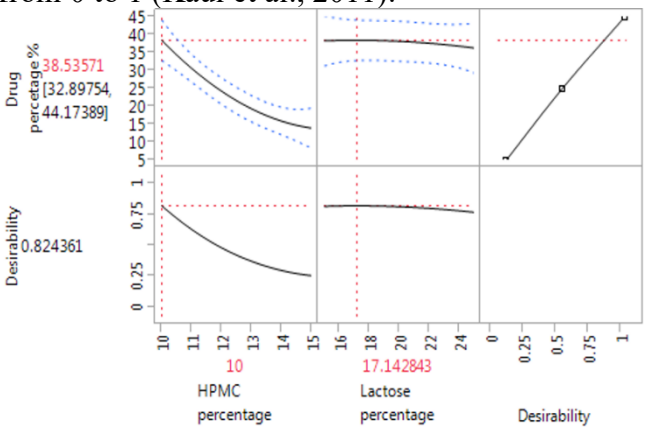


**Figure 13.** Prediction profiler of drug release percentage after the first hour.

A prediction profiler depicts the effect of HPMC K100M and lactose on the drug release percentage after six hours (Figure 14). This figure also illustrates that the percentage of drug release decreased by increasing the concentration of HPMC K100M from 10% to 15% in the formulation. In contrast, an increase in the percentage of the channeling agent (lactose) led to slight changes in the drug release percentage. The value of desirability for the drug release percentage and the two factors at six hours was higher at approximately 0.923.

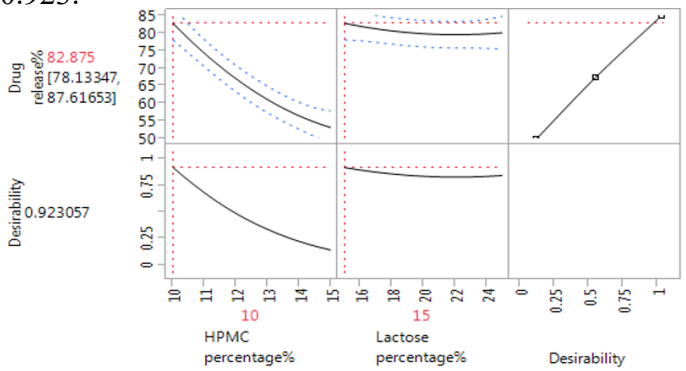


**Figure 14.** Prediction profiler of drug release percentage in 6 hours.

## Response Surface Plots

Response surface design is one of the key tools that offers empirical models (linear, quadratic) that depict the influence of formulation variables or process parameters on the responses (Rekhi et al., 1999). Furthermore, it is used to assess the impact of variables on the responses studied, and established on the model of two- and three-dimensional plots to statistically evaluate the significant interactions (Rekhi et al., 1999).

Surface plots showing the effect of HPMC K100M and lactose are shown after the first hour in Figure 15. The plot clearly shows that polymer had a greater influence on the response compared to lactose after one hour. After the first hour, the drug release percentage decreased drastically with an increase in polymer concentration, while an increase in lactose concentration did not have a very significant impact on the drug release percentage in one hour.

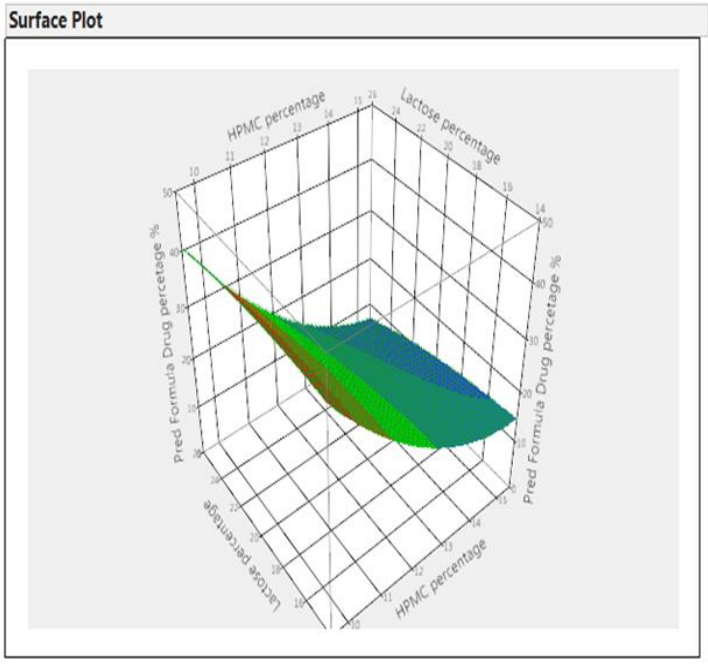


**Figure 15.** Surface plot showing the effect of formulation variables HPMC K100M and lactose on drug release percentage after the first hour.

Figure 16 shows the surface plots showing the effect of HPMC K100M and lactose concentrations on mefenamic acid release after six hours. The plot also clearly illustrates that HPMC K100M had a significant impact on the response. An increase in the concentration of HPMC K100M in the formulation led to a sharp decrease in the release in six hours, but varying concentrations of lactose did not seem to produce a significant change in the drug release percentage. Some authors found that an increase in HPMC K100M significantly influenced the release of tizanidine hydrochloride at eight hours (Kerns and Di, 2008). In addition, Bose et al. (2013) found a similar impact of HPMC K100M on the release of itopride SR from the matrix tablet.

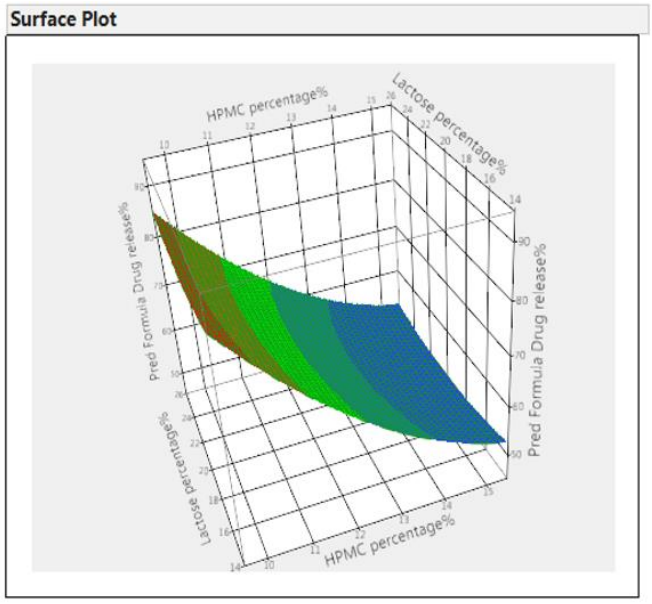


**Figure 16.** Surface plot showing the effect of formulation variables HPMC K100M and lactose on drug release percentage in 6 hours.

## Contour Plots

The objective of pharmaceutical formulation optimization is generally to identify the ranges of input variables that could produce a robust product with high quality (Basalious et al., 2011). The design space could be identified from the common region of the optimal levels of the formulation variables for the response (drug release percentage). Figures 17 and 18 show the contour plots, which were used to demonstrate the design space of the formulation of the mefenamic acid extended-release tablets. They are very useful tools to study the interaction impacts of the independent variables on the responses (Singh et al., 2012).

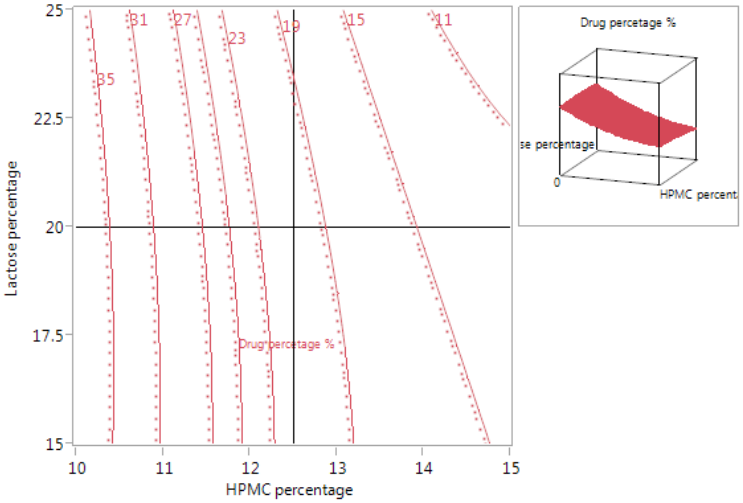


**Figure 17.** Contour plot of the drug release percentage in one hour.

The contour plot of the drug release percentage of mefenamic acid after the first hour is depicted in Figure 17. The figure reveals that the percentage of drug release is acceptable over the HPMC K100M concentration of 10–15% and lactose concentration of 15–25% in one hour. The percentage of drug release was 11% to 35% for all regions, with the contour plot showing it met the aims of QTPP (after the first hour, the drug release percentage was 5% to 54%).

A contour plot of drug release percentage in six hours is shown in Figure 18. This figure illustrates that the percentage of drug release ranged from 54% to 82% when the HPMC K100M concentration was 10–15% and the lactose concentration was 15–25% at six hours. The figure also shows a significant decrease in the drug release percentage with increasing HPMC K100M levels in the mefenamic acid formulations. The drug release percentage was 54–82% in six hours for all regions of the contour plot, demonstrating that at all concentrations of HPMC K100M and lactose studied, tablets were produced meeting the QTPP goals (drug release percentage of 50–85% in six hours). According to Basalious et al. (2011), the levels of input variables within the design space are not considered as an alteration and almost always give the required product quality with optimal critical quality attributes.

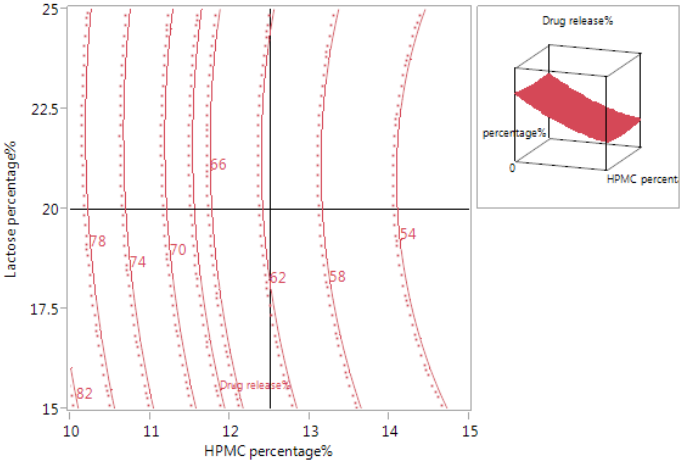


**Figure 18.** Contour plot of the drug release percentage in six hours.

## Interaction Profiles

Figures 19 and 20 show the presence or absence of interactions between the two formulation variables and how their interactions influenced the drug release percentage of the mefenamic acid tablets in one hour and in six hours.

Figure 19 presents the interaction profile for the drug release percentage at different concentrations of HPMC K100M and the channeling agent after the first hour. The interaction profile illustrates the effect of HPMC K100M levels and lactose levels on the drug

release percentage. A higher concentration of HPMC K100M shows a larger decrease in the drug release percentage. In contrast, increasing lactose concentrations at one hour leads to a very small increase in drug release percentage. In addition, the interaction profile clearly demonstrates there is no interaction between the two variables, as these variables are represented as parallel lines in the interaction profile at one hour. The drug release percentage was from 11% to 35% after the first hour for all HPMC K100M and lactose concentrations studied, meeting the QTPP goals of a drug release percentage of 4% to 45% in one hour.

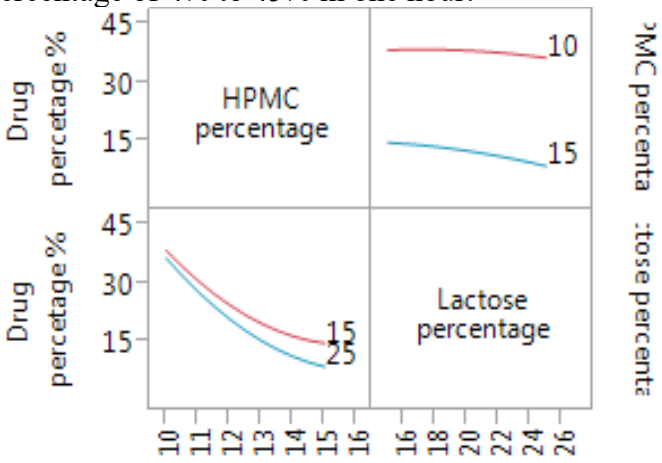


**Figure 19.** Interaction profiles of the drug release percentage with two formulation variables (HPMC K100M concentration and lactose concentration) after the first hour.

Figure 20 reveals the interaction profile for a series of two-dimensional plots exhibiting the impact of interaction between the two formulation variables (HPMC K100M concentration and lactose concentration) on the drug release percentage in six hours. From Figure 20, it can be seen that there is no interaction between the HPMC concentration and lactose concentration, as both lines are parallel. Furthermore, this interaction profile illustrates that the lactose concentration had a minor effect on the drug release percentage at six hours. However, there was a significant decrease in the drug release percentage with an increase in HPMC K100M. The percentage of drug release was between 50% and 85% for all HPMC K100M and the chosen lactose concentrations, meeting the quality attribute target criterion of a drug release percentage of 50–85% in six hours.

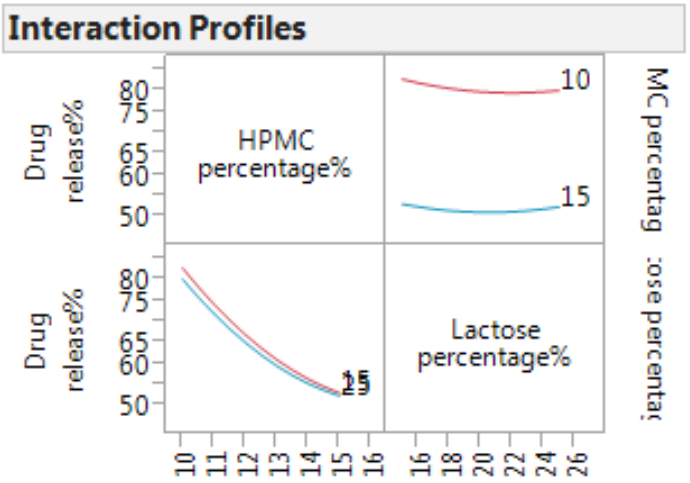


**Figure 20.** Interaction profiles of drug release percentage with two formulation variables (HPMC K100M concentration and lactose concentration) in six hours.

From the above findings, it can be observed that HPMC K100M had a greater influence on the drug release percentage compared to the channeling agent (lactose). An increase in HPMC K100M in the mefenamic acid formulations caused a sharp decrease in the drug release percentage in one hour and in six hours, but lactose did not have a very significant impact on the matrix release. This indicates that the amount of polymer is an important factor in the modified-release formulation that could control the rate of drug release and the mechanism of drug release (Skoug et al., 1993). It has been reported that the HPMC level had a significant effect on the release of metoprolol tartrate compared to other variables (such as filler level, lubricant level, and lubricant blend time) (Rekhi et al., 1999).

Formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, and F12 were evaluated for critical quality attributes (CQAs) using the hardness/thickness tester, friability tester, and dissolution apparatus. It was found that all mefenamic acid formulations were within the acceptable limits for physicochemical parameters. Therefore, it can be concluded that mefenamic acid extended-release tablets can effectively be prepared using different concentrations of the polymer (HPMC K100M) and channeling agent (lactose) using the direct compression method. The drug release percentage for all formulations of mefenamic acid designed met the QTPP goals of 4% to 45% drug release in one hour and 50% to 85% drug release in six hours, respectively. Furthermore, formulations containing 12.5% HPMC K100M and 20% lactose gave the best controlled-release profiles.

## Conclusion

In the present research, Quality by Design (QbD) has proven to be a very useful approach in the development of extended-release formulations for poorly water-soluble drugs (mefenamic acid) based on hydrophilic matrix tablets. This research clarifies the utilization of QbD, including the focus on the importance of Quality Target Product Profiles (QTPP) in elucidating a quantitative performance target for the mefenamic acid formulation. Moreover, implementing risk assessment tools helped identify all potential variables that may influence the quality of the tablets. The control strategy provided assurance to maintain the variables (such as polymer and channeling agent levels, mixing time) within the approved design space and hence ensured that the product met the QTPP goals. Design of Experiment (DoE) was successfully applied for the design and development of mefenamic acid extended-release formulation by allowing rapid and reliable screening to identify the significant formulation variables affecting the drug release percentage, as well as optimization to determine their best concentration for the desired drug release profile.

Mefenamic acid formulations with extended-release characteristics were successfully prepared using different concentrations of polymer (HPMC K100M) and channeling agent (lactose). The results indicated that HPMC K100M had a greater effect on drug release percentage compared to lactose in both one hour and six hours. Formulations containing 15% HPMC K100M (F2, F3, F9) released between 10–20% of mefenamic acid in one hour and approximately 40–55% of the drug in six hours, demonstrating strong retarding effects. Formulations containing 12.5% HPMC K100M (F1, F5, F6, F8, F10, F12) released between 15–30% in one hour and approximately 60% in six hours, providing optimal extended-release profiles. Formulations containing 10% HPMC K100M (F4, F7, F11) released more than 30% in one hour and approximately 70–80% in six hours, indicating insufficient control of drug release. The optimized formulations containing 12.5% HPMC K100M and 20% lactose (F1 and F12) exhibited the most desirable release profiles, with approximately 15–20% release in one hour and 55–60% release in six hours, meeting the QTPP goals of 4–45% release in one hour and 50–85% release in six hours.

All mefenamic acid formulations were within acceptable limits for physical properties (hardness: 6.07–7.63 kg/cm²; friability: <0.4%; thickness: 2.62–2.69 mm; diameter: 5.89–5.96 mm). The drug release percentage for all formulations met the QTPP goals, confirming their suitability as extended-release tablets. HPMC K100M concentration was identified as the critical formulation variable influencing drug release, while lactose concentration had a comparatively minor effect. The interaction profiles confirmed no significant interaction between HPMC K100M and lactose, indicating that these variables act independently in controlling drug release.

In conclusion, the matrix tablets prepared with HPMC K100M (12.5%) and lactose (20%) represent the optimal system for twice-daily extended release of the poorly water-soluble drug mefenamic acid, thus reducing the frequency of administration and increasing patient compliance. This study successfully demonstrated that the application of QbD principles and DoE provides a valuable framework for the rational design and optimization of extended-release dosage forms for poorly water-soluble BCS Class II drugs with short biological half-lives.

Figure 21. Mefenamic acid extended-release tablets.

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