

Development and Evaluation of HPMC-Based Metformin Sustained-Release Tablets

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Abstract. The short half-life and poor patient compliance of conventional metformin formulations necessitate the development of sustained-release (SR) tablets that maintain stable plasma concentrations and reduce dosing frequency. This study aimed to develop and evaluate metformin SR tablets using hydroxypropyl methylcellulose (HPMC K100M) as the primary matrix-forming polymer. Tablets were prepared by wet granulation and compression, with microcrystalline cellulose (MCC) as a filler and magnesium stearate as a lubricant. In vitro dissolution tests were performed via a pH-shift protocol: 2 hours in pH 1.2 hydrochloric acid, followed by 10 hours in pH 6.8 phosphate buffer, and drug content was quantified using a validated HPLC method. The tablets exhibited satisfactory appearance, hardness, and friability, complying with pharmacopeial standards. HPMC content significantly modulated the release rate. Formulations with 20% (F2) and 30% (F3) HPMC provided sustained release over 12 hours, with cumulative releases of $98.5 \pm 1.2\%$ and $95.8 \pm 1.5\%$, respectively. The release kinetics of the optimal formulation (F2) were best fitted to the first-order model ($R^2 = 0.994$), and the release mechanism was classified as non-Fickian (anomalous) transport, indicating a combination of diffusion and polymer erosion. The developed metformin SR tablet, particularly formulation F2, demonstrates promising in vitro performance for twice-daily administration, potentially enhancing patient compliance.

Keywords: metformin, sustained-release tablets, hydroxypropyl methylcellulose (HPMC), formulation optimization, drug release kinetics

1. Introduction

Diabetes mellitus is a global chronic metabolic disease with a continuously rising prevalence, which has led to significantly increased market demand for oral hypoglycemic drugs. Among various antidiabetic agents, metformin is widely used in clinical practice due to its proven efficacy and favorable safety profile. However, conventional immediate-release tablets typically require administration two to three times daily, causing inconvenience for long-term therapy. In recent years, the development of sustained-release drug delivery systems has become a key research direction for improving patient compliance. Previous studies have demonstrated that hydrophilic gel-forming polymers like hydroxypropyl methylcellulose (HPMC) can effectively modulate drug release rates [1], thereby achieving stable and prolonged plasma concentrations. Therefore, to address the limitations of conventional metformin tablets, this study aimed to design and

systematically evaluate an HPMC-based sustained-release metformin tablet, aiming to improve patient convenience by reducing dosing frequency. The research methodology involved formulation screening via a single-factor experimental design, optimization of manufacturing processes (including granulation and compression), and systematic in vitro dissolution testing to evaluate release behavior. This study mainly adjusted the HPMC grade and dosage as well as other excipient ratios to obtain an optimal drug release profile that satisfies sustained-release design criteria. This study holds clear practical significance and application value for optimizing diabetes treatment regimens and improving the long-term management of chronic disease patients.

2. Formulation and process development

2.1. Selection of excipients

The formulation comprised metformin hydrochloride as the model drug (500 mg per tablet, consistent with the clinical routine dose), HPMC K100M as the sustained-release matrix, microcrystalline cellulose (MCC) as a filler/dry binder, and magnesium stearate as a lubricant [2]. HPMC K100M, a high-viscosity grade (approximately 100,000 cP), was selected as the core matrix-forming polymer. Its high viscosity enables the formation of a robust and consistent gel layer upon hydration, effectively controlling drug diffusion and release, a feature that is crucial for achieving a sustained-release effect. Three different HPMC concentrations (10%, 20%, and 30%) were established to analyze the specific effect of polymer content on the drug release profile. MCC, a commonly used excipient, acted as a filler and dry binder, providing excellent compressibility and flowability. This helped address potential tableting challenges associated with high drug and HPMC loads, ensuring adequate tablet hardness and maintaining an ideal state for controlled dissolution. Magnesium stearate was employed as a lubricant at a concentration of 0.5% (w/w). This lubricant reduces interparticulate friction and adhesion to tooling faces, ensuring a smooth tableting process and facilitating compliance with pharmacopeial standards for tablet weight variation.

2.2. Wet granulation and compression parameters

A well-established wet granulation and compression process [3], known for its suitability for industrialization and scale-up with good reproducibility, was adopted.

Mixing and granulating: First, mix the 80-mesh metformin raw material, HPMC K100M and MCC in a high-speed shear granulator for 15 minutes to ensure that each component is uniformly distributed. Then, an appropriate volume of purified water was slowly added as the binder (approximately 20% of the total material weight), and granulation proceeded at a set shear rate. The purpose of wet granulation is to increase the particle size of the powder, improve flowability, and give the particles a certain mechanical strength. **Drying and whole:** The resulting wet particles were placed in a fluidized bed dryer and dried at 60°C to a moisture content of less than 3%. After drying, the particles are aggregated using an oscillating sieve, and a 20-mesh sieve is selected to obtain particles with uniform particle size distribution, which is conducive to subsequent mixing and tablet pressing. **Total mixing and tablet compression:** Mix the whole dry particles with MAGNESIUM STEARATE in a double cone mixing barrel for 10 minutes to ensure uniform distribution. Finally, a single-punch tablet press is used for tablet pressing, and the tablet weight is controlled at about 600 mg by adjusting the filling depth and pressure, and the tablet hardness is maintained within the range of 5-7 kp, with a brittleness of less than 0.8% to meet the requirements of subsequent in vitro tests.

3. In vitro evaluation methods

3.1. Dissolution test conditions

An in vitro dissolution method simulating the gastrointestinal pH environment was established to evaluate the sustained-release performance of the formulations. The test was performed using an intelligent dissolution apparatus (e.g., Distek 2100C). To simulate the transit from stomach to intestine, the test commenced with 900 mL of 0.1 mol/L hydrochloric acid solution (pH 1.2) for 2 hours. Subsequently, 250 mL of preheated 0.2 mol/L tribasic sodium phosphate solution was added to adjust the medium pH to 6.8 ± 0.05 , and the test continued for an additional 10 hours, resulting in a total duration of 12 hours. The dissolution volume was 1150 mL during the intestinal phase (pH 6.8). The temperature was strictly maintained at 37 ± 0.5 °C, and the paddle rotation speed was set to 50 rpm to minimize hydrodynamic shear on the gel layer, thereby reflecting a more diffusion/dissolution-controlled release process. 5mL aliquots were collected from the dissolution medium at preset time points (0.5, 1, 2, 3, 4, 6, 8, 10 and 12 h). An equal volume of fresh pre-warmed medium was replenished immediately after each sampling to maintain sink conditions. The withdrawn samples were filtered through a 0.45 µm membrane filter before HPLC analysis.

3.2. HPLC method validation for drug assay

Chromatographic Conditions: A C18 column (250 mm × 4.6 mm, 5 µm) was used. The mobile phase was a mixture of acetonitrile and phosphate buffer (pH 3.0) (10:90, v/v), with a flow rate of 1.0 mL/min. Detection was performed at 233nm. The column temperature was maintained at 30 °C, and the injection volume was 20µL.

Specificity: The method demonstrated specificity, as the metformin peak (retention time ~4.5 minutes) was well-resolved and showed no interference from excipients or the blank dissolution medium [4]. **Linearity and Range:** The method was linear over the concentration range of 5–200 µg/mL. The standard curve equation was $A = 35214C + 1256.8$, where A is the peak area and C is the concentration in µg/mL. The correlation coefficient (R^2) was 0.9999, indicating excellent linearity [5, 6].

Precision: Intra-day (n=6) and inter-day (n=3 over 3 days) precision were evaluated using quality control samples at low, medium, and high concentrations (20, 80, 160 µg/mL). The relative standard deviation (RSD) at all concentration was below 2.0%, complying with the required limits. **Accuracy:** Determined by the standard addition method, the average recovery of metformin ranged from 98.5% to 101.2% with an RSD of less than 2.0%, confirming high accuracy [7].

Solution Stability: The sample solution was found to be stable for at least 24 hours at room temperature.

4. Results and discussion

4.1. Effect of HPMC content on release profile

The influence of HPMC content on the drug release behavior was investigated by preparing and comparing three formulations (F1: 10% HPMC, F2: 20% HPMC, F3: 30% HPMC).

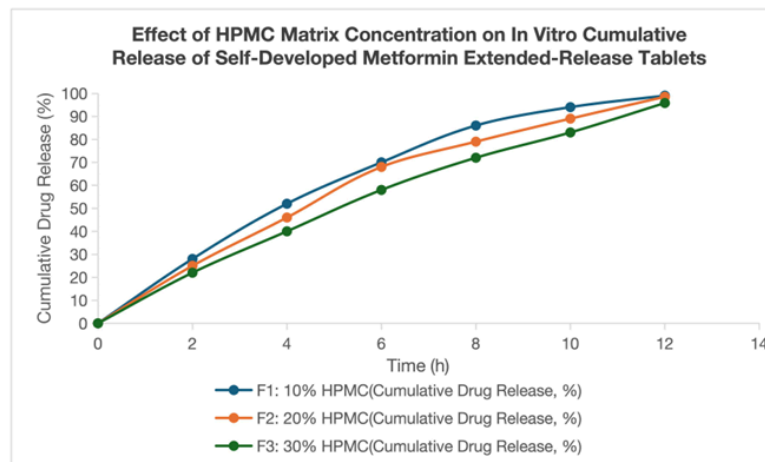


Figure 1. Cumulative release in vitro over time for three different HPMC formulations

As shown in Figure 1, all formulations exhibited an initial burst release (approximately 20-30%) within the first 2 hours in the simulated gastric fluid (pH 1.2), likely due to the rapid dissolution of surface-associated drug before a fully formed gel layer was established. The drug release rate was significantly moderated after transitioning to the intestinal pH (6.8) medium. Formulation F1 (10% HPMC) released the fastest, exceeding 85% cumulative release within 8 hours and thus failing to achieve the targeted 12-hour sustained release. This suggests that the gel layer formed with a lower HPMC content was insufficiently robust to effectively retard drug diffusion. In contrast, formulation F2 (20% HPMC) exhibited ideal sustained-release characteristics, providing a stable and nearly constant release rate over 12 hours, with a cumulative release of $98.5\% \pm 1.2\%$. Formulation F3 (30% HPMC) demonstrated the slowest release rate, achieving a cumulative release of $95.8\% \pm 1.5\%$ over 12 hours. Although sustained release was achieved, the release rate was slower than that of F2, showing a tendency to decelerate further in the later stages. These results indicate that HPMC content is a critical factor controlling metformin release. Within the studied range, increasing the HPMC content led to the formation of a denser and more viscous gel layer, resulting in a longer diffusion path and greater resistance to drug release. Formulation F2 (20% HPMC) achieved the optimal balance under the experimental conditions, providing the desired 12-hour release profile.

4.2. Release kinetics modeling

The dissolution data for the optimal formulation (F2) were fitted to various mathematical models to elucidate the release mechanism.

Table 1. Model fitting parameters for the in vitro release data of formulation F2

Fitting Model	Equation Form	R ²	Characteristic Parameter	Drug Release Mechanism Analysis
Zero-order kinetics	Cumulative release vs. Time	0.962	-	Good fit, indicating an approximately constant release rate over time.
First-order kinetics	$\ln(100 - M_t)$ vs. Time	0.989	-	Best fit, suggesting the release rate is proportional to the remaining drug load in the matrix.

Table 1. (continued)

Higuchi model	Cumulative release vs. $\sqrt{\text{Time}}$	0.973	-	High fit, implying that drug diffusion is a predominant mechanism.
Korsmeyer-Peppas model	$\ln(M_t/M_\infty)$ vs. $\ln(\text{Time})$	0.991	$n = 0.65$	Release exponent n between 0.45 and 0.89 indicates non-Fickian (anomalous) transport, controlled by both diffusion and polymer relaxation/erosion.

The high correlation coefficient ($R^2 = 0.989$) for the first-order model indicates that the drug release rate from the HPMC matrix is proportional to the amount of drug remaining in the tablet. The Higuchi model fit ($R^2 = 0.973$) confirms the significance of diffusion through the hydrated gel layer. The Korsmeyer-Peppas model yielded a release exponent (n) of 0.65, which falls within the range for non-Fickian transport. This suggests that the release mechanism is not governed by diffusion alone but involves a combination of drug diffusion through the gel layer and the simultaneous erosion/dissolution of the polymer matrix itself.

4.3. Comparison with commercial product

The release profile of the optimal formulation F2 was compared with the dissolution profile of a commercially available metformin sustained-release tablet (e.g., Glucophage XR) [8-10], as illustrated in Figure 2. The release rate of F2 was slightly faster than that of the commercial product during the initial 0-4 hours, which might be beneficial for rapidly attaining therapeutic drug levels. However, the release curves were highly similar from 4 to 12 hours, and the final cumulative releases were nearly identical. This comparability in vitro demonstrates the feasibility and effectiveness of the formulation strategy employed in this study.

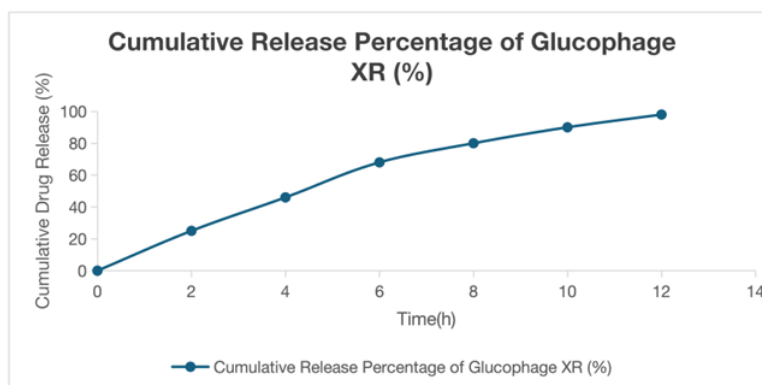


Figure 2. In vitro release profile of formulation F2 compared to a commercial metformin sustained-release product (Glucophage XR)

Note: Commercial product data adapted from literature [10-11].

5. Discussion

The rapid release observed with the 10% HPMC formulation (F1) can be attributed to the formation of a thin and weak gel layer that offers insufficient resistance to drug diffusion and dissolves relatively quickly. Consequently, this formulation failed to sustain drug release over 12 hours. The 20% HPMC formulation (F2) achieved an optimal balance, where the gel layer formed rapidly upon

hydration, effectively regulating drug release without over-restriction, thereby generating a smooth and complete release profile. In contrast, the 30% HPMC formulation (F3) formed an excessively dense gel layer, leading to prolonged water penetration and drug diffusion paths, which slowed the release, particularly in the later stages, posing a potential risk of incomplete release. This demonstrates an inverse relationship between HPMC content and release rate within a certain range, highlighting the existence of an optimal concentration window for HPMC in hydrogel matrix systems, consistent with classical controlled-release mechanisms.

The kinetic modeling further supports these observations. The high fitness to the first-order model is characteristic of hydrophilic gel matrix systems. The non-Fickian release mechanism ($n=0.65$) confirms that drug release is governed by the synergistic effects of diffusion through the gel network and the erosion of the polymer matrix.

6. Conclusion

This study successfully developed and evaluated an oral sustained-release tablet of metformin hydrochloride. Through systematic formulation screening and process optimization, an optimal formulation (F2) containing 20% HPMC K100M as the sustained-release matrix was identified. In vitro dissolution tests confirmed that this formulation achieved stable and continuous drug release over 12 hours, with a cumulative release exceeding 98%. Kinetic modeling analysis demonstrated that the drug release profile best conformed to the first-order model, following a combined diffusion and matrix erosion mechanism. The F2 formulation exhibited a release profile comparable to a commercially available reference product. Therefore, the metformin sustained-release tablets developed in this study show potential for extending the dosing interval and improving patient compliance, providing a solid foundation for subsequent in vivo pharmacokinetic studies and industrial development.

This study has some limitations. Firstly, although the *in vitro* dissolution conditions simulated gastrointestinal pH changes, they cannot fully replicate the complex in vivo environment (e.g., gastrointestinal motility, food effects). Secondly, the study focused on the single-factor effect of HPMC content; future work could introduce more variables (e.g., HPMC grade, other excipient combinations) for more comprehensive formulation optimization, potentially using Design of Experiment (DoE) methodologies. Future research should focus on evaluating the formulation's bioavailability and pharmacokinetics in animal models and conducting bioequivalence studies against commercial products to ultimately confirm its clinical value.

References

- [1] Gao X, Huang DW, Ren Q, et al. Study on matrix material properties and process parameters affecting gel strength of hydrophilic matrix tablets [J]. Chinese Journal of Pharmaceuticals, 2023, 54(3): 383-394+461. DOI: 10.16522/j.cnki.cjph.2023.03.012..
- [2] Amitava R, Kalpana R, Sarbani R, et al. Response surface optimization of sustained release metformin-hydrochloride matrix tablets: influence of some hydrophilic polymers on the release [J]. ISRN pharmaceuticals, 2012, 2012: 364261. DOI: 10.5402/2012/364261.
- [3] Melha M Y, Selma T, Hichem T, et al. Formulation and evaluation of xanthan gum microspheres for the sustained release of metformin hydrochloride [J]. Micromachines, 2023, 14(3): 609. DOI: 10.3390/mi14030609.
- [4] Patel K, Kachhiya T, Patel H, et al. Analytical quality-by-design-oriented high-performance liquid chromatographic method for quantification of metformin hydrochloride, teneligliptin hydrobromide hydrate and dapagliflozin in tablet dosage form [J]. Separation Science Plus, 2026, 9(4): e70235. DOI: 10.1002/sscp.70235.
- [5] Demirović A, Uzunović A, Hamalukić V A. High-performance liquid chromatography method for simultaneous determination of the degradation products of metformin hydrochloride and vildagliptin [J]. European journal of

- pharmaceutical sciences, 2025, 214: 107268. DOI: 10.1016/j.ejps.2025.107268.
- [6] Huang WD. Determination of metformin hydrochloride in cosmetics by high performance liquid chromatography [J]. China Surfactant Detergent & Cosmetics, 2022, 52(8): 863-867.
- [7] Zheng D, Liang AY, Lai ZF, et al. Optimization of methods for related substances inspection and content determination of metformin hydrochloride [J]. West China Journal of Pharmaceutical Sciences, 2026, 41(1): 69-72. DOI: 10.13375/j.cnki.wcjps.2026.01.012.
- [8] Xu K, Jiang JG, Zhu N, et al. Study on dissolution profiles and dissolution rate of generic metformin hydrochloride tablets on the market [J]. China Pharmaceuticals, 2018, 27(22): 28-32.
- [9] Wang YR, Zhang YP, Zhang D, et al. Effects of HPMC from different sources on in vitro and in vivo drug release characteristics of metformin hydrochloride sustained-release tablets [J]. Chinese Journal of Pharmaceuticals, 2019, 50(7): 773-779. DOI: 10.16522/j.cnki.cjph.2019.07.012.
- [10] FDA. GLUCOPHAGE XR (metformin hydrochloride) extended-release tablets [EB/OL]. (2022). http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/21202scf008_glucophage_lbl.pdf
- [11] Yang JR, Zhu Y. Study on in vitro release consistency between self-prepared metformin hydrochloride sustained-release tablets and original drug Glucophage XR [J]. Shanghai Medical & Pharmaceutical Journal, 2017, 38(5): 7-10.