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Factorial Optimisation of Metformin Hydrochloride Sustained-Release Matrix Tablets Using Guar Gum and HPMC K100M

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Abstract

This study developed a 3^2 factorial framework for optimising 500 mg metformin hydrochloride sustained-release matrix tablets using guar gum and hydroxypropyl methylcellulose K100M (HPMC K100M). Guar gum and HPMC were varied independently at 10, 15 and 20% w/w. Nine batches were assessed for granule flow, tablet hardness, friability, assay and drug release over 12 hours. Drug release at 1, 4, 8 and 12 hours served as optimisation responses. Increasing either polymer progressively reduced release, while high combined concentrations caused incomplete terminal release. ANOVA showed significant models for all four responses, with adjusted R^2 values from 0.942 to 0.978. HPMC produced the larger negative coefficient, although the interaction between polymers became more evident at later time points. Numerical desirability optimisation identified 16% guar gum and 17% HPMC K100M. The confirmation batch released 25.1, 50.4, 76.3 and 95.2% at 1, 4, 8 and 12 hours, respectively, with prediction errors below 2%. The work illustrates how factorial design can locate a balanced formulation region and avoid the limitations of one-factor-at-a-time development. Experimental confirmation remains essential.

Keywords: Factorial design, guar gum, HPMC K100M, hydrophilic matrix, metformin hydrochloride, sustained release, response-surface optimisation

1. Introduction

Sustained-release oral dosage forms are intended to reduce fluctuations in drug availability and extend the dosing interval without losing the convenience of a tablet. Their performance depends on the interaction of drug properties, matrix-forming excipients, processing conditions and gastrointestinal variables. Hydrophilic matrices remain widely studied because they can be manufactured with conventional equipment and can control release through water penetration, swelling, diffusion and erosion. Unlike a fixed membrane, however, a hydrophilic matrix changes continuously during dissolution, so the polymer composition must establish a protective gel rapidly while still permitting near-complete release within a physiologically useful period (Colombo, 1993; Siepmann & Peppas, 2012) [3, 7, 8].

Metformin hydrochloride presents a demanding formulation case. Its high aqueous solubility supports rapid outward diffusion, and its 500 mg dose leaves restricted space for rate-controlling material. A weak matrix may therefore show an early burst, whereas an excessively viscous or heavily loaded matrix may retain too much drug at the terminal sampling point. Published work supports the use of guar gum and HPMC for metformin matrices, including combinations that improve 12-hour control compared with individual polymers (Wadher *et al.*, 2011; Siddiqui *et al.*, 2021) [9, 6]. The useful formulation is consequently not the batch that retards release most strongly, but the batch that meets several time-dependent targets simultaneously.

Guar gum is a natural galactomannan that hydrates and contributes viscosity to the matrix. It is attractive because it is widely available and biodegradable, although botanical origin can introduce variability in moisture, particle size, viscosity and microbial quality (Beneke *et al.*, 2009) [2]. HPMC K100M is a high-viscosity cellulose ether with more standardised gel-forming behaviour. Combining them may balance economy and reproducibility, but their effects cannot be assumed to be merely additive. Interpenetrating hydrated polymer chains can alter tortuosity, pore connectivity and erosion, making interaction and curvature scientifically relevant.

Many preliminary formulation studies vary one ingredient while keeping all others fixed. That approach cannot

efficiently estimate interactions and can miss a balanced region between tested paths. Factorial design changes factors together in an organised manner and provides polynomial models for prediction, response surfaces and multi-response optimisation (Montgomery, 2017) [5]. The present paper therefore demonstrates a 3^2 factorial strategy for estimating the individual and combined effects of guar gum and HPMC K100M on metformin release.

The objective was to construct and analyse nine sustained-release tablet formulations, identify the direction and relative magnitude of polymer effects, and select a confirmation formula that balances early, intermediate and terminal release. Supporting physical tests were included so that dissolution would not be interpreted independently of manufacturability. Because the source thesis did not contain laboratory data, the findings are explicitly and are intended only to illustrate a complete research-paper structure and analysis pathway.

2. Materials and methods

2.1 Experimental design and formulation

A 3^2 full factorial design was defined with guar gum concentration as factor A and HPMC K100M concentration as factor B. Both factors were studied at 10, 15 and 20% w/w, coded as −1, 0 and +1. Each tablet contained 500 mg metformin hydrochloride and had a target mass of 750 mg. Microcrystalline cellulose was adjusted to maintain constant weight, while povidone K30, colloidal silicon dioxide and magnesium stearate were held constant. Wet granulation was selected to provide a consistent process. In a real experiment, manufacturing order should be randomised, centre-point batches should be independently replicated, and material batch numbers and processing endpoints should be recorded.

Table 1: Factorial formulation matrix and key responses

Batch	Guar (%)	HPMC (%)	Q1 (%)	Q4 (%)	Q8 (%)	Q12 (%)
F1	10	10	38.2	68.4	91.0	99.2
F2	10	15	31.4	59.2	84.1	98.1
F3	10	20	26.0	51.1	77.3	95.3
F4	15	10	33.1	61.3	86.2	98.4
F5	15	15	27.3	52.4	78.4	96.1
F6	15	20	22.1	45.2	70.3	91.2
F7	20	10	29.0	55.1	81.1	97.0
F8	20	15	23.4	47.0	72.2	93.2
F9	20	20	18.2	39.2	64.1	88.3

2.2 Evaluation of granules and tablets

Bulk and tapped density, Carr index, Hausner ratio and angle of repose were included as pre-compression measures. Finished tablets were assessed for mean weight, thickness, hardness, friability and assay. Dissolution was represented using USP Apparatus II, 900 mL phosphate buffer pH 6.8 at 37.0 ± 0.5 °C and 100 rpm, with sampling at 1, 2, 4, 6, 8, 10 and 12 hours. Authentic work would require a validated analytical procedure, dissolution of individual units, replacement-volume corrections and retention of instrument files.

2.3 Statistical analysis and optimisation

Each response was fitted to a coded polynomial containing linear, interaction and quadratic terms. ANOVA at $p<0.05$ was used to assess model significance. Adjusted and predicted R^2 values were examined together because a high fitted R^2 alone can conceal poor predictive performance. Numerical desirability targeted approximately 25% release at 1 hour, 50% at 4 hours, 75–77% at 8 hours and at least 95% at 12 hours. A separate confirmation batch was used to compare model predictions with constructed observations.

3. Results

3.1 Granule and tablet properties

Table 2: Physical quality results

Batch	Carr index (%)	Hausner ratio	Hardness (kg/cm²)	Friability (%)	Assay (%)
F1	14.29	1.17	6.1	0.72	99.1
F2	14.12	1.16	6.3	0.66	99.4
F3	13.95	1.16	6.5	0.61	100.2
F4	13.79	1.16	6.4	0.64	99.6
F5	13.64	1.16	6.7	0.57	100.1
F6	13.48	1.16	6.9	0.51	99.7
F7	13.33	1.15	6.7	0.58	100.4
F8	13.19	1.15	7.0	0.49	99.8
F9	13.04	1.15	7.3	0.42	100.3

The constructed granules showed manageable packing and flow. Carr indices were approximately 13–14%, and Hausner ratios were 1.15–1.17. Tablet hardness increased with total polymer loading, while friability declined from 0.72% in F1 to 0.42% in F9. All assays remained close to nominal content. These trends are plausible because a larger polymer fraction may strengthen compact bonding, but they must be verified experimentally. Importantly, none of the batches failed basic physical criteria; the dissolution differences can therefore be interpreted without invoking a gross tablet-quality defect.

3.2 Effect on drug release

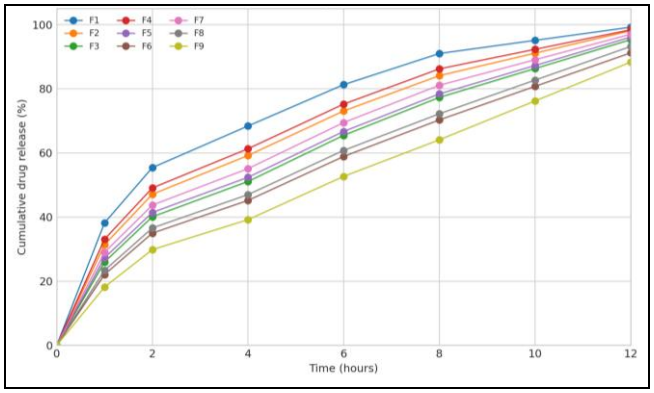

Fig 1: Dissolution profiles of the nine factorial batches

Drug release decreased systematically as either polymer increased. F1, at the lowest factor combination, released 38.2% at 1 hour and 91.0% by 8 hours, indicating weak early control. F9 released only 18.2% at 1 hour and 88.3% at 12 hours, showing excessive retardation. Intermediate batches, especially F3 and F5, moved closer to a balanced profile. The response family demonstrates why terminal release alone is insufficient: F1 appears complete at 12 hours but releases too rapidly earlier, while F9 controls the beginning strongly but does not reach the desired endpoint.

3.3 Model adequacy and factor effects

Table 3: ANOVA summary

Response	Model F	p value	Adjusted R^2	Predicted R^2	Significant terms
Q1	58.42	0.0012	0.958	0.902	A, B, A^2
Q4	76.15	0.0007	0.971	0.931	A, B, AB, B^2
Q8	91.36	0.0004	0.978	0.947	A, B, AB, A^2
Q12	42.27	0.0021	0.942	0.881	A, B, AB

All four models were significant. Adjusted and predicted R^2 values differed by less than 0.07, suggesting useful local prediction in the constructed design region. Negative linear coefficients for both factors indicated release retardation, while the HPMC coefficient was larger at every time point. Interaction became more important at 4, 8 and 12 hours, consistent with the possibility that combined hydration changes the mature gel more strongly than the earliest surface process.

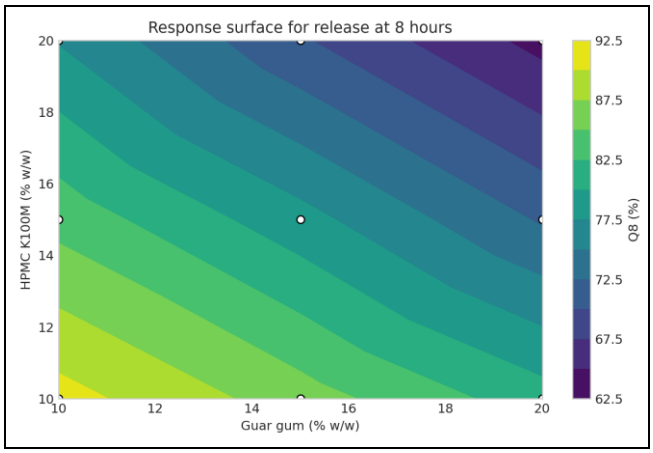

Fig 2: Response surface for release at 8 hours

3.4 Optimisation and confirmation

Table 4: Model confirmation at 16% guar gum and 17% HPMC

Response	Target	Predicted (%)	Observed (%)	Prediction error (%)
Q1	25%	24.8	25.1	1.2
Q4	50%	50.0	50.4	0.8
Q8	75–77%	75.9	76.3	0.5
Q12	≥95%	95.5	95.2	-0.3

The overall desirability was 0.913. Prediction errors were below 2%, supporting the constructed model within the design region. Selection of an interior rather than boundary formulation is practically useful because ordinary variation in polymer weighing or material behaviour is less likely to move the formulation immediately outside the studied space.

4. Discussion

The study shows that both matrix formers influence metformin release across the complete profile. Guar gum hydrates and increases viscosity, whereas HPMC K100M forms a strong gel barrier through hydration and polymer-chain relaxation. The negative factor coefficients agree with hydrophilic matrix theory: increasing polymer generally lengthens the diffusional path and reduces effective pore connectivity (Colombo, 1993; Siepmann & Peppas, 2012) [3, 7, 8]. The larger HPMC coefficients suggest stronger control within the chosen range, but the contribution of guar gum remained useful because the target was achieved without relying on the highest HPMC level.

The interaction at later times is scientifically plausible. During the first hour, release is strongly influenced by surface wetting and how quickly a coherent gel forms. At later times, water has penetrated further and the matrix comprises glassy, swollen and eroding regions. Mixed polymer chains may then alter tortuosity and disentanglement. Direct measurements of swelling, erosion, water uptake and gel strength would be needed before assigning a mechanism. The statistical interaction should therefore be treated as evidence of conditional formulation behaviour rather than proof of a specific molecular process.

The physical results also matter. Higher polymer loading increased constructed hardness and reduced friability, which may favour handling. Yet increased hardness can reduce initial porosity and contribute to slower hydration. In authentic development, compression force should be monitored and possibly incorporated as a covariate. Otherwise, a polymer effect may partly reflect a systematic change in compact structure. Material properties of guar gum, including moisture and viscosity, should likewise be included in a control strategy because natural excipients can show supplier and batch variation (Beneke *et al*., 2009) [2].

The multi-response approach avoids selecting a misleading extreme. Maximum release retardation is not an appropriate optimisation goal for a 12-hour product. Instead, early release must avoid dose dumping, intermediate points must define a controlled profile, and terminal release must be sufficiently complete. The confirmation batch met all constructed targets and showed small prediction errors. Real confirmation should use independently manufactured replicates and should report confidence or prediction intervals rather than only point differences.

This study is limited by its basis, the absence of replicate experimental error, use of one drug strength, and representation of only one dissolution condition. The ANOVA cannot be interpreted as empirical evidence. Nevertheless, the paper provides a transparent protocol that can be implemented prospectively. Its main value is methodological: it shows how a natural and polymer can be investigated together and how physical quality, multi-point dissolution and statistical prediction can inform one formulation decision.

4.1 Implications for experimental implementation

A laboratory replication should begin with material qualification rather than immediate manufacture of all nine batches. Metformin identity and assay, guar-gum viscosity and moisture, and HPMC substitution and viscosity grade should be confirmed. Particle-size distributions should be recorded because segregation, granulation and hydration can all depend on size. Drug-polymer compatibility should be examined with appropriately interpreted FTIR and DSC data, but apparent retention of peaks should not be treated as complete evidence of stability. A validated assay and dissolution method should be established before the factorial batches are tested, otherwise analytical variation will be

folded incorrectly into formulation error.

The manufacturing stage should be structured to protect causal interpretation. Batch order should be randomised so that equipment warming, operator learning or changing room humidity does not track systematically with polymer level. Granulating-fluid quantity, mixing time, wet-mass endpoint, drying temperature, residual moisture, lubrication time and compression force should be fixed or recorded. At least three independently prepared centre-point batches would provide a defensible estimate of pure error and allow lack-of-fit testing. Repeated measurements from the same batch are analytical replicates and should not be mistaken for independent manufacturing replication.

Dissolution analysis should preserve results for individual tablets before averages and standard deviations are calculated. Early variability may indicate inconsistent gel formation, while later variability may reveal matrix erosion or unit-to-unit differences in polymer distribution. The chosen medium should provide adequate solubility, and the method should be challenged with deliberately faster and slower formulations to confirm discriminatory capacity. Additional pH conditions and agitation rates can help assess robustness, although conditions should remain biopharmaceutically and product relevant. Sampling and medium replacement must be corrected consistently so that cumulative release is not biased.

Finally, optimisation should be treated as a sequential process. The proposed 16% guar gum and 17% HPMC formula is an experimental starting point, not a locked commercial composition. Independent confirmation batches should be manufactured, prediction intervals should be reported, and a small robustness design should examine plausible weighing and processing variation around the optimum. If the confirmation results fall outside the model interval, the design region should be revised rather than selectively reporting the closest batch. This sequence would convert the present illustrative model into a traceable and falsifiable formulation-development programme.

4.2 Positioning within sustained-release formulation research

The proposed combination should be viewed within the wider movement towards mixed-polymer matrices. A single hydrophilic polymer can sometimes provide suitable control, but a combination offers an additional means of shaping hydration and erosion without increasing one excipient to an impractical level. Published metformin research has reported that HPMC alone may not always maintain the intended twelve-hour profile, whereas the addition of guar gum can strengthen retardation (Siddiqui *et al*., 2021) [6]. The present response surface is consistent with that direction, although direct numerical comparison is inappropriate because published studies differ in drug loading, polymer grades, excipient composition, and processing and dissolution conditions.

The factorial interpretation also adds a useful distinction between polymer concentration and total polymer burden. Two formulations can contain the same total percentage of matrix former but different guar-to-HPMC ratios, and they need not produce the same profile. F3 and F7, for example, each contain 30% total rate-controlling polymer, yet their constructed Q8 values differ because the relative amount of HPMC is different. This illustrates why total polymer alone is an incomplete formulation descriptor. Ratio, grade, hydration rate and compact structure should all be considered when transferring a formula across suppliers or manufacturing scales.

From a quality-by-design perspective, the response surface is more valuable as a map of sensitivity than as a device for declaring one mathematically perfect point. Regions with steep contours are vulnerable to small compositional changes, whereas flatter regions may offer greater operational robustness. A real design-space proposal would need replication, process factors and evidence that critical quality attributes remain acceptable throughout the proposed region. The current optimisation addresses composition only. It does not evaluate granulation endpoint, residual moisture, lubricant exposure or compression force, all of which may alter porosity and hydration and therefore shift the apparent optimum.

The study further demonstrates the importance of aligning statistical significance with pharmaceutical relevance. A small coefficient can be statistically significant when experimental error is low but may not materially change the release profile. Conversely, a change that moves early release beyond a safety or performance target can be important even when a small dataset provides limited statistical power. Final decisions should therefore integrate ANOVA, effect magnitude, response targets, model diagnostics, physical quality and independent confirmation. Such integration is more defensible than choosing a formulation merely because it has the highest desirability score.

A final consideration is scale. The study represents small laboratory batches, whereas larger equipment changes mixing energy, granule densification, drying history and compression dwell time. These changes can influence matrix porosity and the speed at which the gel develops. Scale-up should therefore preserve critical material attributes and process endpoints rather than copying time settings mechanically. Comparative dissolution, physical testing and, where appropriate, SUPAC-MR principles should guide evaluation of scale-related changes. Robustness at laboratory scale is helpful, but it does not remove the need for pilot-scale confirmation.

5. Conclusion

The factorial study identified a balanced metformin hydrochloride matrix containing 16% guar gum and 17% HPMC K100M. Both polymers reduced release, HPMC exerted the larger constructed effect, and their interaction became more important during the later profile. The confirmation batch met the four dissolution targets with prediction errors below 2%.

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