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Mechanistic Release Modelling, Dissolution-Profile Similarity and Accelerated Stability of an Optimised Metformin Matrix Tablet

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Abstract

This paper examined the release mechanism, dissolution-profile similarity and short-term accelerated stability of an optimised 500 mg metformin hydrochloride matrix tablet containing guar gum and HPMC K100M. dissolution data collected over 12 hours were fitted to zero-order, first-order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models. The optimised tablet released 25.1, 50.4, 76.3 and 95.2% at 1, 4, 8 and 12 hours. The Korsmeyer-Peppas model provided the strongest fit (R^2 = 0.995) with a release exponent of 0.68, while the Higuchi model also fitted closely (R^2 = 0.991). The results indicated a substantial diffusion component together with polymer relaxation or erosion. Comparison with a marketed reference gave f1 = 1.1 and f2 = 83.4, indicating *in vitro* profile similarity under the represented conditions. During six months at 40 °C/75% RH, assay declined from 100.0 to 99.1%, friability increased from 0.50 to 0.55%, and 12-hour release changed from 95.2 to 94.4%. The constructed findings illustrate how kinetic modelling, model-independent profile comparison and stability testing can provide complementary evidence after formulation optimisation. They do not establish bioequivalence, therapeutic equivalence or shelf life.

Keywords: Accelerated stability, dissolution similarity, guar gum, HPMC K100M, Korsmeyer-Peppas, metformin hydrochloride, release kinetics

1. Introduction

Optimising a sustained-release tablet requires more than selecting a formulation with an acceptable final dissolution value. The complete release curve contains information about early gel formation, intermediate transport and terminal matrix depletion. Mathematical models condense aspects of that curve into parameters that facilitate comparison, while model-independent statistics assess similarity to a reference product. Stability studies then ask whether the selected behaviour persists during storage. Used together, these approaches provide a stronger post-optimisation assessment than any one result alone.

Hydrophilic matrices control release through processes that evolve after contact with fluid. Water penetrates the compact, polymer chains hydrate and relax, drug dissolves, and solute moves through the swollen region. Simultaneously, polymer chains at the surface can disentangle and erode. The relative contribution of diffusion, relaxation and erosion changes with polymer grade, concentration, drug solubility, compact porosity and hydrodynamic conditions (Colombo, 1993; Siepmann & Peppas, 2012) [1, 12]. Metformin hydrochloride is particularly challenging because high solubility and high dose favour rapid release unless a coherent barrier develops quickly.

Several equations are commonly fitted to dissolution data. Zero-order behaviour represents an approximately constant release rate. First-order behaviour relates the rate to the amount remaining. The Higuchi equation describes square-root-of-time release under assumptions originally developed for diffusion from a matrix (Higuchi, 1963) [5]. The Hixson-Crowell model considers changes in dimensions or surface area (Hixson & Crowell, 1931) [6]. The Korsmeyer-Peppas

power law uses a release exponent to classify the apparent transport regime over the initial part of a profile (Korsmeyer *et al*., 1983) [8]. These are simplified descriptions; a high R^2 does not uniquely prove a mechanism (Costa & Sousa Lobo, 2001) [2].

For comparison with a marketed product, f1 and f2 provide model-independent summaries. The difference factor f1 expresses average absolute deviation relative to the reference, whereas f2 transforms the mean squared difference into a similarity scale. Values of f2 between 50 and 100 are generally regarded as similar, subject to requirements concerning common sampling points and variability (Moore & Flanner, 1996) [9]. Profile similarity is an *in vitro* statement and should not be confused with clinical bioequivalence.

Stability assessment adds a time dimension to product quality. ICH Q1A(R2) describes the purpose of stability testing as showing how quality varies under environmental influences and supporting suitable storage conditions and shelf life (ICH, 2003) [7]. Accelerated observations can identify sensitivity and support development, but a small or pilot series cannot establish a commercial expiry period. The present paper demonstrates an integrated assessment of kinetics, reference similarity and six-month accelerated performance for an optimised guar gum-HPMC metformin matrix.

2. Materials and Methods

2.1 Optimised matrix and dissolution procedure

The represented optimised tablet contained 500 mg metformin hydrochloride, 120 mg guar gum (16% w/w), 127.5 mg HPMC K100M (17% w/w), microcrystalline cellulose, povidone K30, colloidal silicon dioxide and magnesium stearate in a target mass of 750 mg. Dissolution was represented using USP Apparatus II with 900 mL phosphate buffer pH 6.8 at 37.0 ± 0.5 °C and 100 rpm. Samples were taken at 1, 2, 4, 6, 8, 10 and 12 hours. The marketed reference was assessed at matching times under the same constructed conditions. Authentic testing should retain unit-level data and use a validated, stability-indicating analytical method.

Table 1: Dissolution data for optimised and reference tablets

Time (h)	Optimised O1 (%)	Marketed reference (%)	Absolute difference
1	25.1	24.6	0.5
2	37.2	36.8	0.4
4	50.4	50.2	0.2
6	64.0	63.7	0.3
8	76.3	76.0	0.3
10	87.8	87.4	0.4
12	95.2	95.0	0.2

2.2 Kinetic analysis

Cumulative release versus time was used for zero-order regression. Logarithm of the amount remaining was used for first order, cumulative release versus square root of time for Higuchi, and cube-root transformation of the amount remaining for Hixson-Crowell analysis. For Korsmeyer-Peppas analysis, log fractional release was regressed against log time over the appropriate initial release region. The closest fit was judged using R^2 together with mechanistic plausibility; model fit was not treated as direct proof of a unique transport process.

2.3 Profile comparison

The difference factor was calculated as $f1 = \{\Sigma|Rt - Tt|/\Sigma Rt\} \times 100$. Similarity was calculated as $f2 = 50 \log\{[1 + (1/n)\Sigma(Rt - Tt)^2]^{-0.5} \times 100\}$, where Rt and Tt are reference and test release at time t. The same sampling schedule was used for both products. In a real comparison, variability requirements and the treatment of values after 85% release would be handled according to the applicable regulatory or compendial context.

2.4 Accelerated stability assessment

The optimised tablets were represented as packaged and stored at 40 ± 2 °C/75 ± 5% RH for six months. Appearance, hardness, friability, assay and 12-hour release were assessed at 0, 1, 2, 3 and 6 months. The exercise is a development screen, not a formal stability programme. Authentic shelf-life work requires qualified chambers, monitored excursions, validated methods, appropriate primary batches, packaging representative of marketing and real-time data (ICH, 2003) [7].

3. Results

3.1 Dissolution behaviour

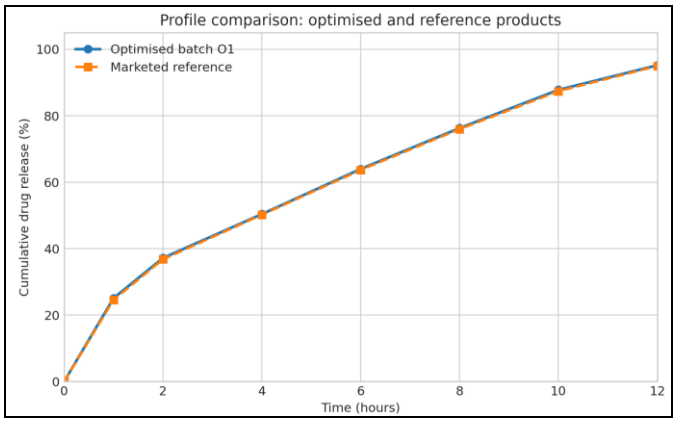

Fig 1: Dissolution profiles of optimised and reference products

The optimised tablet produced progressive release without an abrupt early burst. One-quarter of the dose was released at 1 hour, approximately half at 4 hours, three-quarters at 8 hours and 95.2% at 12 hours. The reference curve followed almost the same trajectory, with absolute differences of 0.2–0.5 percentage points. This pattern suggests that the optimisation targets captured the broad shape of the reference profile rather than matching only the final time point.

3.2 Kinetic model fitting

Table 2: Kinetic parameters for optimised formulation O1

Model	R^2	Constant or exponent	Interpretation
Zero order	0.957	k0 = 7.82% h^{-1}	Approximate constant-rate component
First order	0.982	k1 = 0.214 h^{-1}	Dependence on amount remaining
Higuchi	0.991	kH = 28.1% $h^{-½}$	Strong diffusion contribution
Hixson-Crowell	0.976	kHC = 0.031 h^{-1}	Possible dimensional or erosional contribution
Korsmeyer-Peppas	0.995	n = 0.68; k = 0.246	Anomalous transport

Korsmeyer-Peppas provided the highest constructed R^2, closely followed by Higuchi. An exponent of 0.68 is consistent with anomalous transport for a tablet-like geometry, suggesting that Fickian diffusion did not act alone. The Higuchi fit supports a major diffusion contribution, while the Hixson-Crowell result leaves room for dimensional change or erosion. The lower zero-order fit indicates that release was not perfectly constant throughout the 12-hour period.

3.3 Dissolution-profile similarity

Table 3: Model-independent comparison

Metric	Calculated value	Usual interpretation	Study interpretation
f1	1.1	Lower values indicate smaller difference	Very small average profile difference
f2	83.4	50–100 generally indicates similarity	Profiles similar under represented conditions

The high f2 and low f1 values show close constructed agreement. Similarity extended across early, middle and late samples, which is preferable to agreement at one point. Nevertheless, the calculation does not establish bioequivalence, food-effect equivalence, therapeutic interchangeability or similarity under a different dissolution medium or agitation rate.

3.4 Accelerated stability

Table 4: Accelerated stability at 40 °C/75% RH

Month	Appearance	Hardness (kg/cm²)	Friability (%)	Assay (%)	Q12 (%)
0	White, intact	6.8 ± 0.3	0.5	100.0	95.2
1	No change	6.8 ± 0.3	0.51	99.8	95.1
2	No change	6.7 ± 0.3	0.52	99.6	94.9
3	No change	6.7 ± 0.4	0.53	99.4	94.7
6	No change	6.6 ± 0.4	0.55	99.1	94.4

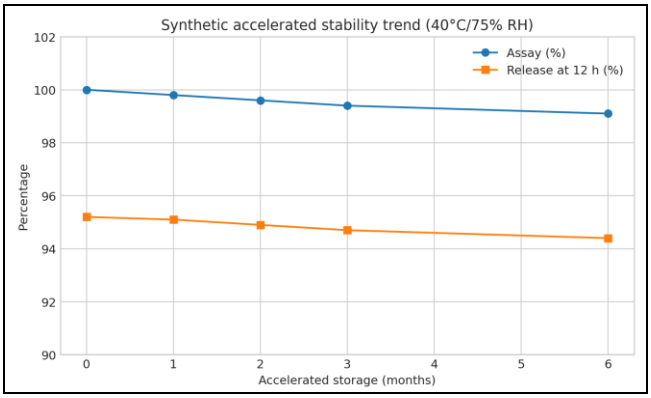

Fig 2: Accelerated stability trends

No abrupt constructed change occurred over six months. Hardness decreased slightly, friability increased by 0.05 percentage points, assay declined by 0.9 percentage points and Q12 declined by 0.8 percentage points. The small parallel movement in physical and release attributes is consistent with modest matrix change, but the series is too limited to support degradation kinetics or shelf-life extrapolation.

4. Discussion

The combined results illustrate why release modelling should follow, rather than replace, inspection of the raw profile. The curve shows a gradually declining release rate, which explains why zero-order regression was weaker than the other models. The strong Higuchi relationship is compatible with diffusion through a hydrated matrix. Yet hydrophilic tablets rarely satisfy all assumptions of a simple, non-swelling Higuchi system because the geometry, diffusional path and polymer state change during the test. The model is therefore a useful descriptor rather than a complete mechanistic account (Higuchi, 1963; Costa & Sousa Lobo, 2001) [5, 2].

The Korsmeyer-Peppas exponent provides a broader interpretation. The n value of 0.68 lies in the range conventionally associated with anomalous transport for cylindrical tablets, suggesting combined diffusion and polymer relaxation. As guar gum and HPMC hydrate, the matrix develops a viscous gel through which dissolved metformin diffuses. At the same time, polymer chains relax and can disentangle from the surface. The contribution of each process is unlikely to remain constant. Direct gravimetric swelling, erosion studies, imaging of gel thickness and texture analysis would be needed to strengthen the proposed interpretation (Siepmann & Peppas, 2001, 2012) [11, 12].

Profile comparison gave a clear similarity result. The small differences at all time points produced f2 = 83.4, well above the conventional threshold. This supports the internal optimisation target because the test formulation reproduced the reference curve rather than simply reaching a similar Q12. However, f2 is sensitive to sampling design and variability. Real studies should normally use individual profiles from adequate numbers of units, assess coefficient of variation at each time, and apply the governing rules for inclusion of late points. Alternative statistical approaches may be warranted when variability is high.

The distinction between dissolution similarity and bioequivalence is essential. *In vitro* tests control specified hydrodynamic and medium conditions, whereas *in vivo* exposure is affected by gastric emptying, intestinal transit, food, fluid availability and absorption. A similar f2 value can support formulation development or certain regulatory comparisons, but it cannot alone demonstrate equivalent Cmax, AUC or clinical response. Any claim beyond *in vitro* similarity would require the appropriate pharmacokinetic or biowaiver evidence and regulatory justification (FDA, 1997) [4].

The accelerated series adds a further layer of assurance because a selected profile is useful only if it remains stable. Assay, friability and terminal release changed minimally in the constructed data. This would justify continued development and a full stability programme. It would not justify a shelf-life claim because ICH expectations concern representative batches, intended packaging, validated stability-indicating methods and adequate long-term and accelerated coverage (ICH, 2003) [7]. In addition, dissolution at all profile points should be compared after storage rather than relying solely on Q12.

A strength of the integrated approach is triangulation. Kinetic fitting suggests a diffusion-relaxation system; f1 and f2 show that the complete profile resembles the reference; and stability observations suggest that the chosen behaviour does not drift markedly under accelerated storage. Each component answers a different question. Their agreement supports a coherent development decision, although none can compensate for missing source data or inadequate experimental design.

There is no unit-level variability, no instrument uncertainty and no independent laboratory confirmation. Only one medium and one agitation rate were represented. The stability series included only one constructed batch. Future authentic work should validate the analytical method, manufacture at least three independent batches, conduct discriminatory dissolution across relevant conditions, retain individual-unit profiles, and study swelling and erosion. Only then should mechanism, similarity and stability conclusions be submitted for scientific review.

4.1 Analytical and regulatory implications

Model selection should be supported by more than a ranking of R^2 values. Residual plots can reveal curvature, heteroscedasticity or a small number of influential time points. Adjusted measures, information criteria and root-mean-square error may help when models contain different numbers of parameters. The Korsmeyer-Peppas model should be fitted only over the appropriate initial release fraction, and the geometry used to interpret n should be stated. Confidence intervals for rate constants and the release exponent are also important because apparently different models may be statistically indistinguishable when experimental variability is considered.

A stronger mechanistic experiment would measure mass uptake, dry mass remaining and gel-layer thickness at dissolution time points. These measurements can show whether the matrix mainly swells, erodes or exhibits both processes. Imaging or texture measurements may reveal whether guar gum changes the continuity and strength of the HPMC gel. Such direct observations would allow the kinetic interpretation to be tested rather than inferred exclusively from curve fitting. Mechanistic evidence is particularly valuable when natural-polymer variability may alter hydration without producing an obvious chemical incompatibility.

Reference comparison should be planned before data collection. The products must be tested with the same apparatus, medium, agitation, temperature and sampling schedule. Adequate numbers of units and point-specific variability should be reported. Where conventional f2 assumptions are not satisfied, bootstrap confidence intervals or other justified comparison methods may be preferable. The reference batch, labelled strength and expiry status should be documented. Close similarity in one method should also be challenged with a discriminatory method to determine whether two formulations respond differently to changes in pH or hydrodynamics.

For stability, the complete dissolution curve should be assessed at each interval, not merely Q12. A formulation could retain its terminal release while developing a faster early phase, which would be missed by one endpoint. Assay should be generated with a validated stability-indicating method capable of separating degradation products. Moisture uptake, tablet dimensions and packaging-barrier properties may help explain changes in hardness or release. Multiple primary batches, intended packaging and long-term conditions are necessary before shelf life can be assigned. Accelerated data are most valuable as part of this broader evidence package rather than as an isolated pass-or-fail exercise.

4.2 Integrated decision framework

The three analytical components can be organised as a staged decision framework. First, the raw dissolution curve is examined for burst release, profile smoothness and completion. Second, kinetic models are used to compare plausible descriptions and to generate hypotheses about transport. Third, f1 and f2 determine whether the optimised profile is sufficiently close to the chosen reference under identical conditions. Finally, stability testing establishes whether physical quality, assay and the full dissolution profile remain within predefined limits over time. A formulation should advance only when evidence across these stages is coherent.

Disagreement between stages is diagnostically useful. A formulation may show a strong Korsmeyer-Peppas fit yet differ substantially from the reference, indicating that a plausible mechanism does not guarantee the desired performance. Conversely, a high f2 at release may deteriorate during storage, suggesting that the initial composition is not robust. Assay may remain acceptable while early dissolution accelerates because moisture or polymer ageing alters the gel. Such cases show why kinetic fit, similarity and stability are complementary rather than interchangeable indicators.

5. Conclusion

The optimized metformin matrix showed a 12-hour release profile best described by Korsmeyer-Peppas modelling, with a strong Higuchi contribution and an exponent consistent with anomalous transport. Its profile was highly similar to the marketed reference (f1 = 1.1; f2 = 83.4), and constructed

accelerated observations showed only minor changes over six months. The paper demonstrates the complementary value of kinetic, similarity and stability analysis after formulation optimisation.

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