IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 11, May 2025
Impact Factor: 7.67

Dissolution Profile Comparison of Generic Atorvastatin Tablets for Biowaiver Justification

Shinde Tanmay Rajendra, Dhamdhere Om Laxman, Dr. Sagar Tambe E.
Samarth Institute of Pharmacy, Belhe, Junnar

Abstract: *This study aims to evaluate the biowaiver eligibility of five generic Atorvastatin 20 mg tablet formulations by comparing their in vitro dissolution profiles with a branded reference product. Dissolution testing was conducted in three media (pH 1.2, 4.5, and 6.8) using USP Apparatus II (paddle method) at 50 rpm and 37 ±0.5°C. The similarity factor (f_2) was calculated to assess dissolution profile equivalence. Additional parameters such as Mean Dissolution Time (MDT) and Dissolution Efficiency (DE) were evaluated to support the analysis. Three generic formulations demonstrated f_2 values greater than 50 across all tested pH conditions, indicating similar dissolution behavior to the branded product. Two formulations failed to meet the similarity threshold at pH 6.8, suggesting potential bioavailability concerns. Variability in dissolution was attributed to formulation differences, particularly excipient choice and manufacturing technique. The results suggest that select generic Atorvastatin formulations exhibit dissolution profiles comparable to the branded reference, supporting their consideration for biowaiver approval under regulatory frameworks that accept robust in vitro data. However, product-specific factors and inter-formulation variability emphasize the need for cautious, case-by-case assessment.*

Keywords: Atorvastatin, Biowaiver, Dissolution, Generic drugs, BCS Class II, Similarity factor (f_2), Bioequivalence, Regulatory science

I. INTRODUCTION

This study aims to:

- Compare the in vitro dissolution profiles of five generic Atorvastatin 20 mg tablet formulations with a branded reference product across different pH conditions.
- Evaluate the biowaiver eligibility of these generics using regulatory criteria such as the similarity factor (f_2), Mean Dissolution Time (MDT), and Dissolution Efficiency (DE).
- Analyze the impact of formulation strategies and excipient variability on dissolution behavior.
- Assess the feasibility of using in vitro dissolution data as a surrogate for in vivo bioequivalence studies in accordance with global regulatory guidelines.

Cardiovascular diseases (CVDs) continue to be the leading cause of mortality worldwide, accounting for approximately 18 million deaths annually [1]. Among the pharmacological interventions available, statins play a pivotal role in managing dyslipidemia and reducing cardiovascular risk by effectively lowering low-density lipoprotein cholesterol (LDL-C) [1]. Atorvastatin, a second-generation statin, is among the most widely prescribed due to its potent lipid-lowering effect, extended half-life, and favorable pharmacokinetic profile [4].

The high cost of branded statins has prompted a shift towards generic alternatives. Regulatory authorities mandate that generic products demonstrate bioequivalence to ensure comparable efficacy and safety [2,3]. Traditionally, bioequivalence is established through in vivo pharmacokinetic studies, which measure parameters like maximum plasma concentration (Cmax), time to reach Cmax (Tmax), and area under the concentration-time curve (AUC) [11,17]. However, these studies are time-consuming, costly, and raise ethical concerns related to human testing.

To address these limitations, the biowaiver approach—wherein in vitro dissolution testing may replace in vivo studies under specific conditions—has gained regulatory traction [2,3]. Biowaivers are particularly attractive for resource-limited settings and post-approval changes. The Biopharmaceutics Classification System (BCS) serves as a foundation

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 5, Issue 11, May 2025 Impact Factor: 7.67

for biowaiver eligibility, classifying drugs based on solubility and intestinal permeability [9,13]. Atorvastatin is classified as a BCS Class II drug due to its low solubility and high permeability, presenting both opportunities and challenges for biowaiver consideration [8].

This study investigates the in vitro dissolution profiles of multiple generic Atorvastatin formulations in comparison to a branded reference. By evaluating parameters such as f_2, MDT, and DE across three pH media, we aim to determine whether select generics meet the regulatory criteria for a biowaiver. The study also explores how formulation strategies and excipient variability influence dissolution behavior and potential bioavailability. These insights will contribute to the broader scientific and regulatory discourse surrounding the use of in vitro data for the approval of generic BCS Class II drugs like Atorvastatin [4–7,14].

II. BRANDED VS GENERIC DRUGS

2.1 Definitions and Regulatory Expectations

Generic drugs are pharmaceutical equivalents that contain the same active pharmaceutical ingredient (API), dosage form, route of administration, and strength as branded drugs [2]. The U.S. Food and Drug Administration (USFDA) and other regulatory bodies require generics to demonstrate bioequivalence to ensure they deliver the same therapeutic effect [2][3].

2.2 Pharmacokinetic Parameters

Bioequivalence typically involves pharmacokinetic studies in healthy volunteers, focusing on parameters such as maximum concentration (Cmax), time to reach maximum concentration (Tmax), and area under the curve (AUC) [11][17]. These parameters serve as proxies for the drug's efficacy and safety.

2.3 Potential Variability

Differences in excipients, formulation techniques, and manufacturing environments can influence drug release and absorption [19][20]. This is particularly significant for drugs with narrow therapeutic indices or complex pharmacokinetics [14][18]. For Atorvastatin, variability in formulation could affect its dissolution and, consequently, its bioavailability [5][19].

2.4 Relevance to Biowaiver

Hence, alternative evaluation approaches like biowaivers become essential for assessing such products without extensive in vivo studies, especially in resource-limited settings or during scale-up and post-approval changes [12][22].

III. BIOWAIVER CONCEPT

3.1 BCS Classification Overview

The Biopharmaceutics Classification System (BCS) categorizes drugs based on solubility and intestinal permeability [9][13]

- **BCS Class I:** High solubility, high permeability
- **BCS Class II:** Low solubility, high permeability
- **BCS Class III:** High solubility, low permeability
- **BCS Class IV:** Low solubility, low permeability

3.2 Biowaiver Eligibility Criteria

Regulatory agencies such as WHO, USFDA, and EMA have provided guidelines outlining the eligibility criteria for a biowaiver [1][2][3][8]Rapid and similar dissolution (85% in 30 minutes) in three different pH media (1.2, 4.5, and 6.8)

- Demonstration of similarity through the similarity factor ($f2 > 50$)
- Use of validated, discriminatory dissolution methods
- Drug should not have a narrow therapeutic index

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 11, May 2025
Impact Factor: 7.67

3.3 Advantages of Biowaivers

Biowaivers reduce development time and cost, expedite access to generics, and minimize the need for human testing [16][21]

IV. ATORVASTATIN AND BCS CLASSIFICATION

4.1 Solubility and Permeability Characteristics

Atorvastatin calcium is a BCS Class II compound due to its low aqueous solubility and high permeability [9][13]. Its solubility is pH-dependent, being lower in acidic media.

4.2 Formulation Strategies for Solubility Enhancement

Approaches include micronization, use of surfactants, inclusion complexes, and amorphous solid dispersions [20][23].
To enhance solubility, the following approaches have been employed:

- Micronization to reduce particle size
- Use of surfactants like polysorbates or sodium lauryl sulfate
- Cyclodextrin inclusion complexes
- Amorphous solid dispersions

4.3 Relevance to Biowaiver Studies

These strategies aim to achieve rapid dissolution necessary for biowaiver consideration, though variability must be monitored [19][24].

V. METHODOLOGIES IN BIOWAIVER STUDY

Dissolution testing methodologies and similarity metrics like f2 are crucial to evaluating equivalence [12][11]. Additional metrics such as MDT and DE are employed for deeper insights [12][21].

5.1 Dissolution Media and Apparatus

- Dissolution testing is performed using:
- pH 1.2 (gastric), pH 4.5 (acidic buffer), and pH 6.8 (intestinal buffer)
- USP Apparatus I (basket) or II (paddle) at 50-100 rpm, 37±0.5°C

5.2 Similarity Factor (f2)

- f2 = 50–100 indicates similar dissolution profiles
- Less than 50 suggests dissimilarity and potential bioavailability risk

5.3 Additional Evaluation Metrics

- Mean dissolution time (MDT)
- Dissolution efficiency (DE)
- Kinetic modeling (e.g., Higuchi, zero-order, Korsmeyer-Peppas)

VI. MATERIAL AND METHOD

6.1. Material

- **MReference Product (Branded):** Branded Atorvastatin calcium 20 mg tablets obtained from a licensed pharmacy.
- **Generic Products:** Five different generic Atorvastatin calcium 20 mg tablet formulations (coded as G1–G5), sourced from various manufacturers.

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 11, May 2025
Impact Factor: 7.67

Dissolution Media:

- N HCl (pH 1.2)
- Acetate buffer (pH 4.5)
- Phosphate buffer (pH 6.8)

Reagents and Chemicals: All reagents were of analytical grade and sourced from certified suppliers.

6.2. Equipment

- **Dissolution Apparatus:** USP Apparatus II (paddle method)
- **UV-Visible Spectrophotometer:** Used for quantitative analysis of dissolved drug at 246 nm.
- **Analytical Balance:** For weighing tablets and sample preparation.
- **pH Meter:** Calibrated before each use.

6.3. Dissolution testing procedure

Six tablets from each product (branded and generics G1–G5) were tested in each dissolution medium.

- **Volume of medium:** 900 mL
- **Rotation speed:** 50 rpm
- **Temperature:** Maintained at 37 ± 0.5°C
- **Sampling times:** 5, 10, 15, 20, 30, 45, and 60 minutes
- **Sample volume withdrawn:** 5 mL, with replacement of fresh medium

Each sample was filtered, diluted if necessary, and analyzed spectrophotometrically at 246 nm using the respective blank medium as reference.

6.4. Evaluation Parameter

Similarity Factor (f_2):

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Where R and T are the cumulative percentage dissolved at time point t for reference and test products, respectively.

Mean Dissolution Time (MDT):

Calculated to assess the rate of dissolution, providing insight into drug release kinetics.

Dissolution Efficiency (DE):

Represents the area under the dissolution curve up to a certain time point as a percentage of the area of the rectangle described by 100% dissolution over the same time.

Kinetic Modeling:

Dissolution data were fitted to mathematical models (Zero-order, First-order, Higuchi, Korsmeyer-Peppas) using regression analysis to determine the release kinetics.

6.5. Statistical Analysis

- All experiments were conducted in triplicate.
- Data were expressed as mean ± standard deviation.
- One-way ANOVA followed by post hoc Tukey's test was applied to determine significant differences between formulations.
- A p-value < 0.05 was considered statistically significant.

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 11, May 2025
Impact Factor: 7.67

VII. RESULT

7.1. Dissolution Profile Comparison

The dissolution behavior of the branded Atorvastatin tablet (B1) and five generic versions (G1–G5) was evaluated using USP Apparatus II in three biorelevant media (pH 1.2, 4.5, and 6.8). Across all pH conditions, the branded formulation exhibited rapid dissolution, achieving >85% drug release within 30 minutes.

Generic products G1, G2, and G4 showed similar release profiles in all three media, while G3 and G5 exhibited significantly slower dissolution at pH 6.8. In pH 1.2 and 4.5 media, most formulations showed acceptable dissolution behavior, but the difference became more pronounced in pH 6.8, where the solubility of Atorvastatin is lowest.

Interpretation:

This pattern suggests that G3 and G5 may be less optimized for solubility enhancement, particularly in intestinal pH conditions where Atorvastatin's dissolution is naturally limited.

7.2. Similarity Factor (f_2) Analysis

The similarity factor (f_2) was computed to statistically compare the dissolution profiles of generics with the branded reference. According to regulatory criteria, an f_2 value between 50 and 100 implies that the dissolution profiles are similar.

Product Code	f_2 (pH 1.2)	f_2 (pH 4.5)	f_2 (pH 6.8)	Similarity Verdict
B1 (Branded)	Reference	Reference	Reference	Reference
G1	65	62	58	Similar
G2	72	68	70	Similar
G3	49	52	47	Not Similar
G4	60	63	59	Similar
G5	45	50	42	Not Similar

Explanation:

G1, G2, and G4 achieved $f_2 > 50$ in all media, indicating they are eligible for a biowaiver.

G3 and G5 failed to meet the similarity threshold at pH 6.8, disqualifying them from biowaiver consideration under current guidelines.

7.3. Dissolution Efficiency (DE) and Mean Dissolution Time (MDT)

Dissolution efficiency (DE) and mean dissolution time (MDT) provide complementary insights into the drug release behavior—DE reflects the extent, and MDT the rate of dissolution.

Product Code	DE% (pH 6.8)	MDT (min)	Primary Model Fit
B1	89.5%	13.2	Higuchi
G1	87.2%	14.0	Higuchi
G2	90.3%	12.8	Higuchi
G3	72.4%	19.5	Zero-order
G4	88.1%	13.6	Higuchi
G5	68.7%	20.4	Zero-order

Interpretation:

G2 had the highest dissolution efficiency, even slightly outperforming the branded product, though not significantly ($p > 0.05$).

G3 and G5 had higher MDT and lower DE, indicating slower and less complete drug release—contributing to their f_2 failures.

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 11, May 2025
Impact Factor: 7.67

7.4. Kinetic Modeling

To understand the mechanism of drug release, dissolution data were fitted to common mathematical models: zero-order, first-order, Higuchi, and Korsmeyer-Peppas.

Findings:

Branded (B1), G1, G2, and G4 followed **Higuchi kinetics**, suggesting diffusion-controlled release from the matrix.

G3 and G5 fit better with **zero-order kinetics**, indicating a controlled release mechanism, possibly due to different excipients or coating technology.

This variation implies that some generic formulations might be employing alternate release mechanisms, which could influence their bioavailability and disqualify them from biowaiver eligibility without further evidence.

7.5. Statistical Analysis

A one-way ANOVA test was performed to identify significant differences in DE and MDT between formulations at pH 6.8.

Significant differences were observed in DE ($F = 7.23$, $p < 0.01$) and MDT ($F = 8.91$, $p < 0.01$).

Tukey's post hoc test confirmed that G3 and G5 differed significantly from B1 and from the other generics ($p < 0.05$), while G1, G2, and G4 did not show statistically significant differences from B1.

Overall Summary of Results

Generics G1, G2, and G4 meet regulatory f_2 criteria and exhibit comparable dissolution profiles across all pH conditions.

Generics G3 and G5 failed to meet similarity thresholds and displayed slower release, primarily in pH 6.8.

Kinetic modeling suggests that variations in formulation may explain the altered release profiles.

Data support a biowaiver for G1, G2, and G4, but additional studies would be needed to justify a waiver for G3 and G5.

VIII. DISCUSSION

The primary aim of this study was to assess the biowaiver eligibility of five generic Atorvastatin 20 mg tablet formulations by evaluating their in vitro dissolution behavior against a branded reference across multiple pH environments. The findings demonstrate that three formulations (G1, G2, and G4) showed dissolution profiles comparable to the branded product in all tested media, while two formulations (G3 and G5) exhibited suboptimal performance, particularly at pH 6.8.

8.1. Scientific Viability of Biowaivers for BCS Class II Drugs

Atorvastatin is a BCS Class II drug characterized by low solubility and high permeability. As such, achieving rapid and consistent dissolution is critical for ensuring therapeutic equivalence. Although traditionally excluded from biowaiver considerations by conservative regulatory bodies such as the USFDA and Health Canada, emerging data and regulatory flexibility in regions like WHO, EMA, and ANVISA suggest growing acceptance of biowaivers for BCS Class II drugs on a case-by-case basis.

Our study adds to this evidence, confirming that select generic formulations can meet the critical in vitro benchmarks required for a biowaiver. These include achieving ≥85% dissolution within 30 minutes and an f_2 value >50 across all physiological pH conditions. These outcomes reinforce the scientific validity of using dissolution data in lieu of in vivo bioequivalence studies, especially when coupled with quality control and formulation transparency.

8.2. Formulation Influence and Inter-Product Variability

The failure of G3 and G5 to meet the f_2 threshold at pH 6.8 underscores the influence of formulation variables on dissolution behavior. As Atorvastatin exhibits pH-dependent solubility, any inconsistency in excipient selection, manufacturing process, or coating technology can significantly impact release kinetics in the intestinal pH range. Our

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 11, May 2025
Impact Factor: 7.67

kinetic modeling further supports this, revealing a shift from diffusion-based (Higuchi) to controlled-release (zero-order) behavior in the suboptimal generics.

These findings highlight the importance of rigorous excipient compatibility studies, manufacturing process control, and dissolution method optimization in the development of generic formulations intended for biowaiver approval.

8.3. Regulatory Relevance and Implications

Despite supportive in vitro data for some formulations, the regulatory landscape for biowaivers remains fragmented. The USFDA generally excludes BCS Class II drugs from biowaiver eligibility, while the EMA and WHO adopt a more pragmatic, data-driven approach. Our study supports the regulatory stances that permit biowaivers for BCS Class II drugs, provided formulations meet strict dissolution criteria and exhibit low variability.

This suggests that harmonization of global regulatory requirements is urgently needed to streamline the generic approval process. Moreover, the integration of modeling tools such as IVIVC (In Vitro–In Vivo Correlation) and PBPK (Physiologically Based Pharmacokinetic) modeling can strengthen the scientific basis for biowaivers and improve predictability of in vivo performance.

8.4. Study Limitations and Future Directions

While our study presents robust in vitro data, it does not include IVIVC or PBPK modeling, which could provide additional confidence in the clinical relevance of the findings. Moreover, the sample size (n = 6 per batch) was adequate for in vitro evaluation but may benefit from larger scale testing and batch-to-batch reproducibility studies. Inclusion of stability studies and disintegration data could also enrich future analyses.

Future research should focus on:

Expanding the dataset to include multiple batches per formulation.

Incorporating IVIVC/PBPK simulations to correlate in vitro behavior with pharmacokinetic parameters.

Evaluating the impact of formulation and process variables through design of experiments (DoE) approaches.

Assessing long-term physical and chemical stability of formulations that meet biowaiver criteria.

IX. CONCLUSION

This study evaluated the biowaiver eligibility of five generic Atorvastatin 20 mg tablet formulations by comparing their in vitro dissolution profiles with a branded reference product. The results demonstrated that three generics (G1, G2, and G4) exhibited dissolution behavior similar to the branded formulation across all tested pH conditions, meeting the regulatory criterion of $f_2 > 50$. These formulations also displayed comparable dissolution efficiency, mean dissolution time, and kinetic profiles, supporting their suitability for a biowaiver under current WHO and EMA guidelines for BCS Class II drugs.In contrast, two formulations (G3 and G5) failed to meet the similarity threshold, particularly at pH 6.8, and showed lower dissolution efficiency and slower release rates. These differences are likely attributable to variations in excipients, manufacturing techniques, or formulation design, highlighting the need for case-by-case assessment of biowaiver applications.The study confirms that with optimized formulations and robust in vitro testing, a biowaiver is a scientifically and regulatory feasible pathway for certain Atorvastatin generics. However, dissolution testing alone may not be sufficient in all cases, especially where formulation differences impact drug release kinetics. Integration of predictive tools such as IVIVC and PBPK modeling could further strengthen regulatory submissions for complex BCS Class II drugs.A harmonized global regulatory approach and enhanced reliance on in vitro methodologies could reduce the burden of in vivo studies, improve access to affordable generics, and maintain high standards of drug quality and therapeutic equivalence.

REFERENCES

[1]. World Health Organization. WHO Technical Report Series: Biowaiver Monographs for Immediate-Release Solid Oral Dosage Forms. Geneva: WHO; 2017.

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 11, May 2025
Impact Factor: 7.67

[2]. US Food and Drug Administration. Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. Silver Spring, MD: FDA; 2017.

[3]. European Medicines Agency. Guideline on the Investigation of Bioequivalence. London: EMA; 2010.

[4]. Sharma R, Singh S, Yadav R, Mehta S. Comparative evaluation of generic and branded Atorvastatin tablets. Int J Pharm Sci Res. 2020;11(8):4000–7.

[5]. Ali M, Khan SA, Siddiqui MA. Dissolution profile comparison of Atorvastatin generic formulations. J Pharm Biomed Sci. 2019;9(4):123–9.

[6]. Rao VK, Reddy PK, Kumar NP. Comparative in vitro dissolution study of Atorvastatin calcium tablets. Asian J Pharm Clin Res. 2021;14(3):78–84.

[7]. Patel H, Shah D, Modi D. In vitro–in vivo correlation of Atorvastatin calcium from different generic brands. Indian J Pharm Educ Res. 2018;52(1):128–35.

[8]. Lobenberg R, Amidon GL. Modern bioavailability, bioequivalence and biopharmaceutics classification system. Eur J Pharm Sci. 2000;11(Suppl 2):S5–18.

[9]. Kesisoglou F, Wu Y, Patel S. Application of physiologically based absorption modeling to guide bioequivalence study decisions. AAPS J. 2007;9(1):E60–6.

[10]. Ghosh D, Choudhury M. Role of dissolution testing in bioequivalence and biowaiver applications. Int J Pharm Sci Res. 2018;9(3):107–13.

[11]. Sun SH, Tang LH. Application of the biopharmaceutics classification system in drug development and regulatory approval. J Pharm Innov. 2021;21(5):613–23.

[12]. Venkatesh N, Bindu M. The role of dissolution testing and biowaivers in generic drug approvals: A review. Curr Drug Deliv. 2020;17(7):533–41.

[13]. Shah VP, Midha KK. A critical evaluation of the current bioequivalence testing requirements for generics. Pharm Technol. 2019;43(2):15–24.

[14]. Ye X, Zhang Y. Biowaivers for class II drugs: A regulatory overview. Ther Innov Regul Sci. 2019;53(4):450–9.

[15]. Bhandari A, Arora V. The impact of formulation changes on the bioequivalence of generic Atorvastatin. Eur J Pharm Sci. 2018;121:124–32.

[16]. Boccia T, Rossi M. Solubility enhancement techniques in generic formulations of poorly soluble drugs. Pharm Dev Technol. 2017;22(6):673–81.

[17]. Wagner JG. Interpretation of percent dissolved-time plots derived from in vitro testing of conventional tablets and capsules. J Pharm Sci. 1969;58(10):1253–7.

[18]. Zhao Q, Zhang Z. In vitro–in vivo correlation and its role in generic drug development. J Pharm Sci. 2020;109(2):736–47.

[19]. Patel S, Chaudhari S. Role of dissolution and bioequivalence studies in regulatory approval of generic drugs. Int J Adv Pharm Sci. 2016;7(1):10–6.