

COMPARATIVE STUDY OF TELMISARTAN TABLETS IN STANDARD AND GENERIC DOSAGE FORMS

**Saurabh Milind Bansode¹, Rupesh Bhagwan Sonune², Rushikesh Gajanan Narwade³,
Rushikesh Purushottam Tayde⁴, Sarthak Rajesh Lokhande⁵, Sahil Ramajan Chaudhari⁶,
Sahil Gulab Naurangbadi⁷, Prof. Vishal Hule⁸, Dr. R.R. Pagore⁹**

¹⁻⁷ Student, Bachelor of Pharmacy; ⁸ Professor; ⁹ Principal

Karmayogi Tatyasaheb Bondre Institute of Pharmacy, Chikhali, Buldhana, Maharashtra, India – 443201

ABSTRACT

Telmisartan is an angiotensin II receptor blocker (ARB) widely used in oral antihypertensive therapy. Its formulation development is scientifically important because telmisartan has very low aqueous solubility and strongly pH-dependent dissolution behaviour. The present expanded review develops the original manuscript into a more detailed, evidence-linked discussion of the comparative pharmaceutical performance of reference and generic telmisartan tablets. Particular emphasis is placed on active pharmaceutical ingredient (API) properties, critical material attributes, excipient selection, tablet manufacture, mechanical quality, disintegration, dissolution, similarity assessment, analytical testing, biorelevant dissolution, in-vitro–in-vivo relationships, and bioequivalence. The review also considers recent research that has moved from conventional compendial dissolution toward multi-stage and biopredictive approaches. Published comparative studies show that tablets containing the same labeled strength can nevertheless display measurable differences in dissolution and absorption-related behaviour. Borbás et al. demonstrated sensitivity to excipient substitutions, while Ruiz Picazo et al. showed that an appropriately designed two-step dissolution method could reproduce the rank order of in-vivo behaviour among formulations. Quality-by-design work has further identified binder, disintegrant and wetgranulation conditions as influential variables. More recent studies have emphasized API particle size, polymorphism, microenvironmental pH, dissolution-medium volume and dynamic dissolution testing. The evidence does not support treating brand or generic status alone as a surrogate for quality. Instead, product-specific assessment integrating pharmacopeial quality testing, assay, dissolution, impurity characterization and, where required, pharmacokinetic bioequivalence provides a more defensible basis for comparison. This review identifies current knowledge gaps and proposes future directions involving biorelevant dissolution, dissolution–permeation testing, physiologically based pharmacokinetic modelling and multi-batch comparative evaluation.

INDEX TERM: Telmisartan; angiotensin II receptor blocker; generic tablets; Micardis; dissolution; bioequivalence;

pharmaceutical equivalence; critical material attributes; quality by design; biorelevant dissolution.

I. INTRODUCTION

Telmisartan is a non-peptide angiotensin II receptor blocker that selectively antagonizes the angiotensin II type 1 (AT1) receptor. By preventing angiotensin II from activating AT1 receptors, it reduces vasoconstrictor and aldosterone-secreting effects of the renin–angiotensin system. The FDA prescribing information describes telmisartan as having substantially greater affinity for AT1 than AT2 receptors and notes that its mechanism does not depend on inhibition of angiotensin converting enzyme. [1] The clinical use of telmisartan makes consistent dosage-form performance important because the active ingredient must be liberated from the tablet, dissolve in gastrointestinal fluid, become available for absorption and subsequently reach systemic circulation. From a formulation-development perspective, telmisartan is a useful model for studying poorly water-soluble immediate-release products. The drug is practically insoluble in water and over much of the pH range encountered in aqueous media, while becoming more soluble under strongly basic conditions. [1] Published formulation studies have therefore classified telmisartan as a BCS Class II compound, characterized by low aqueous solubility with comparatively high permeability. [2,3] For such compounds, dissolution can become a rate-limiting step in oral absorption, so apparently small changes in particle size, solid-state form, excipient functionality or local formulation pH can influence product performance.

The comparison of reference and generic tablets is more complex than verifying the labeled dose. Pharmaceutical equivalence concerns the identity, strength, dosage form and route of administration, whereas bioequivalence addresses the rate and extent to which the active ingredient becomes available systemically under defined study conditions. In-vitro dissolution provides an important mechanistic and

quality-control tool, but it is not automatically interchangeable with an *in vivo* bioequivalence conclusion. The original manuscript correctly emphasizes that physical testing, assay, dissolution and pharmacokinetic evidence are complementary rather than redundant. Rationale for the expanded review The initial nine-page manuscript summarized the principal comparative literature but left several areas suitable for deeper treatment: drug physicochemistry, mechanisms by which excipients alter dissolution and absorption, analytical methods, interpretation of f_2 , biorelevant dissolution, quality-by-design, stability, regulatory concepts and future formulation strategies. This expanded version retains the original scope and terminology while integrating additional peer-reviewed and regulatory evidence through 2026.

Objectives

- To describe the physicochemical and biopharmaceutical characteristics that make telmisartan formulation-sensitive.
- To explain how API attributes, excipients and manufacturing variables influence tablet quality and dissolution.
- To critically summarize comparative studies of reference and generic telmisartan products.
- To discuss conventional and biorelevant dissolution approaches and their relationship to *in-vivo* performance.
- To clarify the distinction between pharmaceutical equivalence, dissolution similarity and bioequivalence.
- To identify research gaps and practical future directions for generic telmisartan development.

II. Drug Profile and Pharmacological Background

Parameter Description Generic name Telmisartan Therapeutic class Angiotensin II receptor blocker (ARB) Primary therapeutic use Hypertension; additional indications depend on product labeling and jurisdiction Route Oral Common tablet strengths 20 mg, 40 mg and 80 mg Reference product used in comparative literature Micardis® Biopharmaceutical relevance Poor aqueous solubility; pH-dependent dissolution; commonly studied as BCS Class II Key formulation concern Dissolution and subsequent absorption

2.1 Mechanism of action

Angiotensin II is a major effector peptide of the renin–angiotensin system. Activation of AT1 receptors contributes to vasoconstriction, stimulation of aldosterone secretion, cardiac effects and renal sodium reabsorption. Telmisartan selectively blocks angiotensin II binding to AT1 receptors, thereby reducing these pressor and aldosterone-related actions. Unlike ACE inhibitors, telmisartan does not inhibit ACE and therefore does not directly inhibit bradykinin degradation. [1]

2.2 Pharmacokinetic characteristics relevant to formulation

Following oral administration of the reference product, peak plasma concentrations are generally reached within approximately 0.5–1 hour. The FDA label reports dose-dependent absolute bioavailability and a terminal elimination half-life of approximately 24 hours. Telmisartan is highly bound to plasma proteins. Food has a relatively modest effect on exposure at the commonly used 40-mg dose, although the magnitude varies with dose. [1] These characteristics help explain why immediate-release tablet performance is primarily discussed in terms of liberation, dissolution and absorption rather than prolonged-release control.

2.3 Physicochemical features

The FDA labeling describes telmisartan as a white to slightly yellowish solid that is practically insoluble in water and in the pH range of approximately 3–9, with greater solubility in strong base. The marketed Micardis tablet contains sodium hydroxide, meglumine, povidone, sorbitol and magnesium stearate as inactive ingredients and is described as hygroscopic, requiring protection from moisture. [1] These details are directly relevant to comparative formulation science because the reference product uses excipients that can create a microenvironment favourable to dissolution of a poorly soluble drug.

2.4 Biopharmaceutical implications

For a low-solubility, high-permeability compound, increasing the amount of drug that dissolves at the site of absorption may be more important than simply increasing total tablet disintegration speed. A tablet can disintegrate rapidly while still producing limited dissolved drug if the API remains in an unfavourable solid state or encounters a medium in which solubility is low. Thus, formulation evaluation should connect tablet-level observations to API-level and dissolution-level mechanisms.

III. Physicochemical and Biopharmaceutical Basis of Telmisartan Formulation

3.1 Solubility and pH dependence

Telmisartan exhibits pronounced pH-dependent solubility. Its low intrinsic solubility can restrict the amount available for dissolution in aqueous gastrointestinal environments, whereas alkalization can improve apparent solubility. This property is central to the formulation strategy of the reference product and to the development of generics. A formulation containing an alkalizing or salt-forming component may create a local environment in which dissolution is enhanced, even though the free drug itself remains poorly soluble. The importance of pH is demonstrated by comparative dissolution research. Pande et al. evaluated marketed 40-mg telmisartan products in media at pH 1.2, 4.5, 6.8 and 7.5 and reported product-to-product differences in drug release. [7] The findings illustrate that a formulation may not have a single, universal dissolution ranking; the observed performance can change with the medium. This is particularly important when interpreting generic comparisons performed under only one dissolution condition.

3.2 BCS Class II behaviour

Experimental solubility and permeability work incorporated into the two-step IVIVC study of Ruiz Picazo et al. supported classification of telmisartan as a BCS Class II compound. [2] In BCS Class II systems, low solubility and relatively high permeability make dissolution a potentially important determinant of oral exposure. This does not mean that every formulation difference produces a clinically meaningful difference, but it does mean that formulation development should investigate dissolution mechanisms rather than rely exclusively on tablet appearance or assay.

3.3 Supersaturation and precipitation

When a formulation promotes rapid dissolution through an alkalized microenvironment, the dissolved drug may subsequently encounter a lower-pH environment after gastric emptying. Telmisartan can therefore undergo a pH-shift process involving dissolution, supersaturation and precipitation. Eriksen et al. showed that the volume and composition of biorelevant dissolution media can materially affect precipitation and permeation of telmisartan from combination tablets. [9] Such observations demonstrate why large-volume compendial tests, although valuable for routine quality control, may not always reproduce the dynamic gastrointestinal environment.

3.4 Solid-state considerations

Particle size, surface area, crystallinity and polymorphic characteristics can influence wetting, dissolution rate and formulation reproducibility. The 2026 work by Pillai, Shah and Sengupta evaluated seven telmisartan formulations and linked critical material attributes such as API particle size, excipient composition and polymorphic characteristics with dissolution behaviour.

[8] Their work supports a development philosophy in which the formulation is understood as a system of interacting material and process variables rather than a simple mixture of API and excipients.

IV.4. Reference and Generic Formulations

Micardis® has served as the reference product in several published formulation and bioequivalence investigations. The existence of a reference product does not imply that all generic products should have identical excipient compositions. Generic development instead aims to reproduce the relevant quality and performance attributes under applicable regulatory requirements. The original manuscript identifies filler, binder, disintegrant, alkalizing or salt-forming components, API particle-size distribution and manufacturing conditions as potential sources of formulation differences.

4.1 Role of excipients

Excipients can influence powder flow, wetting, granule formation, tablet strength, porosity, disintegration and local pH. In telmisartan, their role can extend to drug dissolution and membrane permeation. Borbás et al. compared a reference product with four generic formulations and found that changing formulation additives altered the in-vitro dissolution–absorption profile. Substitution of sorbitol with mannitol was associated with an approximately 10% reduction in membrane flux; changing the salt-forming agent was associated with an approximately 20% reduction; and additional lactose monohydrate produced an approximately 10% reduction. [4] These findings show that excipient substitution should be treated as a mechanistic variable rather than as a purely qualitative difference.

4.2 Manufacturing process

Wet granulation can alter particle-size distribution, granule density, porosity and the way the tablet interacts with dissolution medium. In the quality-by-design study of telmisartan potassium tablets, binder level, disintegrant and wet-granulation kneading time were identified as influential variables affecting disintegration, hardness, friability, dissolution and impurities.

[6] These variables can interact. For example, stronger granules may improve mechanical integrity but may also change disintegration behaviour if the formulation becomes too cohesive or less porous.

4.3 Reference product versus generic product

The scientifically useful question is not simply whether a product is branded or generic, but whether the product meets its intended quality and performance characteristics. The original review found that several marketed-product studies reported compliance with stated pharmacopoeial specifications while other investigations detected measurable differences in dissolution or absorption-related behaviour. Therefore, generic status alone should not be used as a proxy for either superiority or inferiority.

4.4 Comparative testing strategy

- Confirm identity and labeled strength.
- Evaluate appearance, dimensions, weight variation, hardness and friability.
- Measure disintegration and assay/drug content.
- Generate dissolution profiles under justified conditions.
- Evaluate f_2 only when the data and study design satisfy the applicable requirements.
- Characterize impurities and degradation products when relevant.
- Use pharmacokinetic bioequivalence data when equivalence is being established in vivo.

V. Quality Control Tests for Telmisartan Tablets

Routine quality-control testing provides the first level of comparative characterization. The tests should be interpreted collectively because no single parameter describes the entire performance of an immediate-release tablet. The original manuscript lists appearance and dimensions, weight variation, hardness, friability, disintegration, assay, dissolution, similarity factor, impurity profile and pharmacokinetic assessment as complementary parameters. N Ö Ö L726

5.1 Appearance and dimensions

Appearance provides rapid information about tablet integrity, defects, coating or surface abnormalities. Thickness and diameter may be affected by tooling, compression, granule density and formulation composition. Although appearance is not a surrogate for bioavailability, major differences may indicate manufacturing variability and should trigger investigation.

5.2 Weight variation

Weight variation provides an indirect measure of dose uniformity when the blend is sufficiently homogeneous and the tablet manufacturing process is controlled. Differences in fill weight can arise from poor flow, segregation or machine settings. For a low-dose drug, weight variation should be considered alongside assay and content uniformity rather than interpreted alone.

5.3 Hardness and friability

Hardness reflects resistance to crushing and can be influenced by compression force, binder concentration, moisture and granule properties. Friability assesses the tendency of tablets to lose mass through abrasion and mechanical stress. Excessive hardness can sometimes delay disintegration, while inadequate mechanical strength can cause handling and packaging problems. The optimal formulation balances robustness with rapid and reproducible drug release.

5.4 Disintegration

Disintegration is the breakdown of a tablet into smaller fragments after contact with liquid. It is an important step before dissolution but should not be equated with complete drug release. Disintegrant type, concentration, granule structure, compression pressure and tablet porosity all influence the process. In telmisartan formulations, a rapidly disintegrating tablet can still display slow dissolution if the liberated API has poor solubility.

5.5 Assay and content uniformity

Assay determines the amount of active ingredient in a sample relative to the labeled claim. Chromatographic methods are particularly useful when the formulation contains degradation products or excipients that could interfere with direct spectrophotometric measurement. Content uniformity assesses dosage-unit consistency and is important for ensuring that individual tablets provide comparable doses.

5.6 Impurity testing

Impurity profiles can reflect API quality, formulation chemistry, manufacturing conditions and storage. The QbD study of telmisartan potassium tablets identified impurities as a risk-related quality attribute alongside dissolution. [6] Consequently, a comparative review should not treat dissolution as the only meaningful performance endpoint.

VI. Dissolution Testing and Interpretation

Dissolution testing measures the rate and extent of drug release from a dosage form into a defined medium. For poorly soluble drugs, it is both a routine quality-control test and a formulation-development tool. Telmisartan is particularly informative because dissolution changes substantially with pH and because formulation components can alter the local chemical environment surrounding the API.

6.1 Conventional dissolution

Compendial apparatus such as USP Apparatus I and II are commonly used because they provide standardized hydrodynamic conditions and are suitable for quality control. However, conventional methods frequently employ relatively large volumes of medium to maintain sink conditions. Eriksen et al. noted that 500–900 mL volumes are commonly used in compendial testing, whereas such volumes are much larger than gastrointestinal fluid volumes and may therefore limit physiological relevance for biopredictive testing. [9]

6.2 Similarity factor f_2

The similarity factor f_2 is a model-independent statistical approach commonly used to compare dissolution profiles when the underlying data and study design meet the relevant regulatory conditions. A higher f_2 indicates greater similarity between two profiles. However, f_2 should not be used mechanically. Sampling-time selection, number of time points, variability, assay

performance and the proportion of dissolved drug all influence the interpretation. The original manuscript appropriately cautions that f_2 should be considered within the complete experimental design rather than as a standalone number.

6.3 Multi-pH dissolution

Telmisartan dissolution should be considered across acidic and near-neutral conditions because the drug's solubility is pH dependent. Pande et al. reported differences among marketed 40-mg tablets across pH 1.2, 4.5, 6.8 and 7.5. [7] Ruiz Picazo et al. developed a three-stage dissolution environment changing from pH 1.2 to 4.5 and 6.8 and found that this model better reproduced the in-vivo rank order among the formulations studied. [2]

6.4 Why dissolution profiles can differ

- API particle size changes effective surface area.
- Different solid-state forms may have different dissolution behaviour.
- Alkalizers and salt-forming components can change microenvironmental pH.
- Fillers and binders can alter wetting, porosity and matrix structure.
- Disintegrants control tablet breakup and expose new surfaces.
- Compression force changes porosity and liquid penetration.
- Medium pH, ionic strength, surfactant level and volume influence apparent solubility.

VII. Comparative Literature Review

7.1 Borbás et al., 2018

Borbás and colleagues investigated one brand and four generic telmisartan formulations using simultaneous dissolution–absorption experiments and in-vivo bioavailability information. The study demonstrated that relatively small formulation changes could influence membrane flux. The authors reported approximately 10% lower flux after changing sorbitol to mannitol, approximately 20% lower flux after changing the salt-forming agent, and approximately 10% lower flux with additional lactose monohydrate. [4] The work is important because it connects excipient selection to an absorption-related endpoint rather than stopping at conventional dissolution.

7.2 Ruiz Picazo et al., 2018

Ruiz Picazo et al. examined Micardis and generic immediate-release formulations using dissolution testing and a two-step Level A IVIVC strategy. One generic formulation demonstrated in-vivo bioequivalence, whereas other test formulations did not meet the bioequivalence acceptance criteria. The study identified a USP IV, three-stage pH-change dissolution method as more predictive of the observed in-vivo formulation ranking. [2] This provides a strong example of how dissolution method development can support formulation selection.

7.3 Bayas et al., 2019

Bayas et al. evaluated four marketed telmisartan tablets for physical characteristics, drug content, disintegration and dissolution. The study reported acceptable tablet properties and pharmacopoeial compliance, with all four products achieving at least 80% drug release within one hour under the reported conditions. [10] This illustrates an important point: marketed products can meet routine quality specifications even when other studies under different conditions reveal formulationspecific differences.

7.4 Quality-by-design study

Oh et al. used a quality-by-design approach to develop telmisartan potassium tablets and compared them with Micardis. The study identified dissolution and impurities as risky CQAs and used risk assessment and design-of-experiments approaches to define influential process and formulation variables. Binder, disintegrant and wet-granulation kneading time affected multiple CQAs, demonstrating the interconnected nature of tablet formulation. [6]

7.5 Pande et al., 2024

Pande et al. compared marketed 40-mg telmisartan tablets with Tazloc using dissolution testing at multiple pH values. The study found product-to-product differences in release. For example, the published report described higher release for Tazloc than selected comparator brands under several test conditions. [7] Because these observations are in-vitro and productspecific, they should not be generalized to all telmisartan products or interpreted as proof of clinical superiority.

VIII.Recent Evidence: Biopredictive Dissolution and Critical Material Attributes

8.1 Pillai, Shah and Sengupta, 2026

The 2026 European Journal of Pharmaceutics and Biopharmaceutics study represents a major extension of the formulationdevelopment approach. Seven telmisartan formulations were examined using multiple analytical techniques, including chromatography, hot-stage microscopy, NMR spectroscopy and dissolution testing. The study organized formulations according to API particle size, excipient functionality and microenvironmental pH, and investigated USP Apparatus I, II and IV for development of a biopredictive method. [8] The reported particle-size groupings included d90 values of approximately $8 \pm 2 \mu\text{m}$, $12 \pm 2 \mu\text{m}$ and greater than $15 \mu\text{m}$. The authors proposed a multi-stage dissolution strategy reflecting acidic gastric and neutral intestinal conditions under fasting conditions. The study

therefore moves beyond the question 'Does the tablet dissolve?' toward the more useful questions 'Why does it dissolve differently?' and 'Will the observed difference be relevant to absorption?' [8]

8.2 Eriksen et al., 2025

Eriksen and colleagues studied two brands of telmisartan/amlodipine tablets using biorelevant dissolution–permeation experiments with different medium volumes. They observed that lower dissolution volumes promoted precipitation of telmisartan and reduced permeation, whereas larger volumes did not produce the same precipitation behaviour. The authors concluded that both volume and composition of the medium can be important when designing biomimetic experiments for supersaturating systems. [9]

8.3 Dynamic 'dumping' dissolution test

Cossio et al. evaluated a dynamic dumping test as a predictive tool for immediate-release telmisartan formulations. The test transferred the product from 20 mL of dilute hydrochloric acid to 480 mL of pH 6.8 phosphate buffer and was linked to a one-step Level A IVIVC. The reported f_2 values were 46.47 for a non-bioequivalent comparison and 57.43 for a bioequivalent comparison. [11] This study illustrates how a dynamic, physiologically motivated dissolution transition may distinguish formulations more meaningfully than a single static condition.

8.4 Integrated interpretation

Taken together, the recent evidence supports an integrated framework: characterize the API, understand excipient functions, map material attributes to CQAs, use appropriately discriminating dissolution methods and connect the in-vitro findings with pharmacokinetic or permeation evidence. This approach is consistent with the research gap identified in the original manuscript, which calls for stronger links between critical material attributes, dissolution and bioequivalence.

IX. Formulation Variables Affecting Telmisartan Tablet Performance

Variable Potential effect Comparative significance API particle size Changes surface area and dissolution rate May change release ranking among formulations Polymorphic/solid-state form Changes thermodynamic stability and dissolution Can influence apparent solubility and reproducibility Alkalizer/salt-forming agent Raises local pH or alters ionization May strongly affect dissolution and absorption Filler Affects wetting, porosity and microenvironment Substitution can change membrane flux Binder Changes granule strength and tablet integrity Can influence disintegration and dissolution Disintegrant Controls tablet breakup Type/concentration can alter release Kneading/granulation time Changes granule structure and density Identified as a QbD variable Compression force Changes porosity and mechanical strength May slow liquid penetration if excessive Dissolution medium Controls pH, wetting and solubility Can change apparent product ranking Storage humidity Can affect hygroscopic formulation components May alter hardness, disintegration and stability

9.1 API particle size

Reducing particle size generally increases specific surface area and can accelerate dissolution when the process remains surface-area controlled. However, particle size is not an isolated determinant. Agglomeration, surface energy, electrostatic behaviour and changes in powder flow may offset the expected benefit. The 2026 Pillai study demonstrates why particle-size distribution should be measured and linked to dissolution rather than treated as a simple numerical specification. [8]

9.2 Alkalization and microenvironmental pH

Because telmisartan is more soluble in strongly basic conditions, formulation components that create an alkaline microenvironment can improve dissolution. The reference formulation includes sodium hydroxide and meglumine, illustrating the practical use of formulation chemistry to manage poor solubility. [1] However, excessive alkalization or an inappropriate salt-forming strategy can create new issues such as precipitation after pH shift or altered impurity behaviour.

9.3 Granulation and compression

Wet granulation determines granule size, density and internal structure, while compression converts the granules into a mechanically stable tablet. These steps control porosity and liquid penetration. QbD research on telmisartan potassium tablets identified binder, disintegrant and kneading time as important variables affecting multiple CQAs. [6] Therefore, optimization should be based on a multidimensional design space rather than on a single target such as maximum hardness.

X. Analytical Methods for Comparative Evaluation

10.1 UV-visible spectrophotometry

UV-visible spectrophotometry is frequently used for dissolution quantification because it is relatively rapid and economical. Pande et al. quantified telmisartan using UV-visible measurements at wavelengths around 291 and 296 nm under their selected conditions. [7] For routine comparative dissolution, the method should be validated for specificity, linearity, accuracy, precision and robustness under the intended medium.

10.2 HPLC

High-performance liquid chromatography is preferred when separation of telmisartan from degradation products, excipients or formulation-related impurities is necessary. HPLC can support assay, related-substance testing and stability- indicating analysis. The broader ARB quality/cost literature summarized in the original manuscript also uses chromatographic characterization as part of a comprehensive product comparison.

10.3 FTIR and NMR

Fourier-transform infrared spectroscopy can provide information about functional groups and potential drug–excipient interactions. Nuclear magnetic resonance spectroscopy can provide complementary information about molecular environment and formulation composition. These tools are particularly useful during formulation development when a difference in dissolution needs to be traced to a material-level cause.

10.4 XRPD, DSC and hot-stage microscopy

X-ray powder diffraction is commonly used to investigate crystalline structure and polymorphic form, while differential scanning calorimetry provides information about thermal transitions and possible interactions. Hot-stage microscopy can help visualize melting or phase transitions during heating. The 2026 Pillai study used orthogonal techniques to characterize critical material attributes and relate them to dissolution. [8]

10.5 Dissolution–permeation systems

Dissolution–permeation methods attempt to connect drug release with the subsequent movement of dissolved drug across a membrane. They can be particularly informative for formulations that undergo supersaturation and precipitation. Borbás et al. used simultaneous dissolution–absorption testing to show formulation-related differences that were not fully explained by conventional dissolution alone. [4]

10.6 Method validation and data integrity

A comparative study should use a validated analytical method, calibrated instruments, controlled temperature and justified sampling times. Raw dissolution data should be retained, and any exclusions or outliers should be predefined according to the study protocol. Transparent reporting is essential because inappropriate sampling or analytical variability can produce an apparent formulation difference that is not truly attributable to the product.

XI. Bioequivalence and In-Vitro–In-Vivo Relationships

Pharmaceutical equivalence, therapeutic equivalence, dissolution similarity and bioequivalence are related concepts but should not be treated as synonyms. Pharmaceutical equivalence focuses on the dosage form and active ingredient characteristics, while bioequivalence is generally established through pharmacokinetic comparison under defined conditions. Dissolution testing is an in-vitro tool and does not by itself establish clinical equivalence. The original manuscript emphasizes this distinction and notes that formulation differences can be associated with pharmacokinetic differences.

11.1 Pharmacokinetic endpoints

Typical pharmacokinetic comparisons consider measures such as maximum plasma concentration (C_{max}) and area under the concentration–time curve (AUC). Ruiz Picazo et al. combined plasma concentration profiles with deconvolution and fraction dissolved measurements to construct a two-step Level A IVIVC for telmisartan. [2] Their work showed that an in- vitro method can be useful when it captures the formulation-dependent processes that govern absorption.

11.2 Why conventional dissolution may fail to predict absorption

A conventional dissolution test may use a fixed pH, large volume and constant hydrodynamics. In the gastrointestinal tract, however, pH changes with location and time, fluid volumes are smaller, bile components can alter solubilization, and dissolved drug can precipitate after a pH shift. For telmisartan, these processes are particularly important because of pHdependent solubility and supersaturation behaviour. [2,9]

11.3 Level A IVIVC

A Level A IVIVC seeks a point-to-point relationship between an in-vitro dissolution process and an in-vivo absorption process. The telmisartan literature provides examples of exploratory and predictive Level A approaches. Ruiz Picazo et al. used a two- step strategy, while the 2025 dumping-test study reported a one-step Level A correlation using a dynamic transfer process. [2,11]

11.4 Interpretation of generic-product differences

If two formulations display different dissolution profiles, the next question is whether the difference is sufficiently large, reproducible and mechanistically relevant to alter systemic exposure. Conversely, similar dissolution under a nondiscriminating method does not

guarantee that all relevant differences have been captured. Therefore, the strongest development strategy uses several levels of evidence: material characterization, tablet testing, dissolution, permeation where appropriate and pharmacokinetic bioequivalence when required.

XII. Quality-by-Design Approach for Telmisartan Tablets

Quality by Design (QbD) is a systematic development approach that begins with a predefined quality target product profile and identifies critical quality attributes, critical material attributes and critical process parameters. For telmisartan, QbD is especially appropriate because multiple formulation and process variables can influence dissolution simultaneously.

12.1 Quality Target Product Profile

- Immediate-release oral tablet containing the intended telmisartan strength.
- Consistent identity, assay and dosage-unit uniformity.
- Acceptable mechanical properties for handling and packaging.
- Rapid and reproducible disintegration appropriate to the dosage form.
- Robust dissolution across justified quality-control conditions.
- Impurity and degradation-product levels within applicable limits.
- Reproducible performance across manufacturing batches.

12.2 Critical Quality Attributes

Potential CQAs include assay, content uniformity, dissolution, disintegration, hardness, friability, water content, impurity profile and stability. The Oh et al. QbD study specifically identified dissolution and impurities as risky CQAs and used risk assessment and design-of-experiments methods to investigate the variables controlling them. [6]

12.3 Critical Material Attributes

For telmisartan, relevant CMAs include API particle-size distribution, solid-state or polymorphic characteristics, excipient grade, alkalizing capacity, binder functionality and disintegrant performance. The 2026 study by Pillai et al. demonstrated a practical CMA–CQA framework by classifying formulations according to particle size, excipient type and microenvironmental pH and relating these characteristics to dissolution. [8]

12.4 Critical Process Parameters

Potential CPPs include blending time, granulation endpoint, kneading time, drying conditions, milling, lubrication time and compression force. The significance of these variables depends on the specific formulation. A robust process should be designed so that normal manufacturing variability does not push the product outside its acceptable performance range.

12.5 Design of Experiments

Design of experiments can identify main effects and interactions more efficiently than changing one factor at a time. The published telmisartan QbD work used a face-centered central composite design after risk assessment. [6] A similar strategy can be used to optimize binder, disintegrant and granulation variables while monitoring dissolution, hardness, friability and impurities as simultaneous responses.

12.6 Control strategy

A control strategy may include incoming-material specifications, in-process controls, compression monitoring, finished product testing and stability monitoring. For a poorly soluble drug, the control strategy should ensure not only dose accuracy but also reproducible dissolution performance.

XIII. Stability, Packaging and Storage Considerations

Stability is an essential component of comparative pharmaceutical quality because a tablet that initially meets specifications must continue to meet them throughout its labeled shelf life. Telmisartan formulations can contain hygroscopic components, and the FDA labeling for Micardis notes that the tablets require protection from moisture. [1] Moisture exposure may change tablet mechanical properties, disintegration, chemical stability and, depending on the formulation, dissolution.

13.1 Physical stability

Physical stability includes maintenance of appearance, hardness, friability, dimensions and disintegration. Changes in moisture content can alter tablet strength and porosity. A formulation may become harder or softer during storage, potentially changing liquid penetration and dissolution. Comparative stability studies should therefore include both physical and performance-related measurements.

13.2 Chemical stability

Chemical stability is monitored through assay and degradation-product testing. A stability-indicating chromatographic method is preferable when degradation products must be separated from the parent drug. The QbD literature identifies impurities as a meaningful

quality attribute in telmisartan formulation development. [6]

13.3 Packaging

Moisture-protective packaging is particularly relevant for hygroscopic products. The package should be selected based on moisture transmission characteristics, storage conditions and intended shelf life. Differences in packaging between products can also influence the stability profile and should be considered when comparing marketed formulations.

13.4 Stability-indicating dissolution

Dissolution should be considered during stability assessment when changes in formulation microstructure or chemical state could influence release. A product can retain acceptable assay while developing a different dissolution profile, especially if storage changes particle agglomeration, tablet porosity or excipient functionality.

13.5 Practical comparative-stability framework

- Evaluate initial and stored samples under defined temperature and humidity conditions.
- Record assay, degradation products and relevant physical parameters.
- Monitor disintegration and dissolution at selected stability time points. ° Use the same validated analytical

procedure across comparison points.

- Investigate any shift in dissolution together with moisture, hardness and impurity data.
- Interpret results according to the approved product specification and applicable regulatory requirements.

The original review appropriately identifies storage and stability conditions among the formulation factors that can affect telmisartan performance. L190N Ö Ö ô

XIV. Integrated Comparative Discussion

The collective evidence demonstrates that telmisartan tablet performance is a multidimensional property. Two products may contain the same active ingredient and labeled strength and still differ in excipient functionality, API particle size, microenvironmental pH, granule structure, tablet porosity and dissolution behaviour. These differences do not automatically imply a clinically meaningful difference, but they justify product-specific characterization when formulation performance is being studied.

14.1 What the literature consistently supports

- Telmisartan has very low aqueous solubility and pronounced pH dependence. [1,2]
- Formulation additives can influence dissolution and absorption-related flux. [4]
- Different generic formulations can show different in-vivo bioequivalence outcomes in specific comparative studies. [2]
- Marketed tablets can comply with routine pharmacopoeial specifications while displaying product-specific

dissolution differences under other conditions. [7,10]

- Binder, disintegrant and granulation conditions can affect multiple quality attributes. [6]
- Biorelevant and dynamic dissolution methods may provide more mechanistic information than a single conventional

test. [2,8,9,11]

14.2 What should not be overgeneralized

Results from a limited number of brands, batches or dissolution conditions should not be generalized to every telmisartan product. For example, a product that released more drug than another brand in one pH condition cannot automatically be described as clinically superior. Similarly, an f_2 result obtained under one method does not establish universal equivalence or non-equivalence. The original manuscript explicitly identifies the need for standardized head-to-head studies and warns against generalizing results from one formulation or market.

14.3 Proposed comprehensive evaluation workflow

- Step 1: Confirm API identity, assay and key material attributes.
- Step 2: Characterize particle size and solid-state properties.
- Step 3: Compare excipient composition and functional roles.
- Step 4: Evaluate tablet physical quality and disintegration.
- Step 5: Conduct dissolution at justified acidic and near-neutral conditions.
- Step 6: Compare profiles using appropriate statistical tools such as f_2 when valid.

- Step 7: If needed, use dissolution–permeation or dynamic pH-shift testing.
- Step 8: Relate in-vitro results to pharmacokinetic evidence and bioequivalence.

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