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Comparison of Multimedia Dissolution and Release Kinetics for a Bilayer Fixed-Dose Combination Tablet: Efonidipine Hydrochloride Ethanolate, Chlorthalidone, and Telmisartan

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ABSTRACT

Introduction: The study was designed to assess the in vitro dissolution behavior, similarity, and drug release kinetics of a bilayer fixed-dose combination (FDC) tablet containing efonidipine hydrochloride ethanolate (Efo), chlorthalidone (Chlor), and telmisartan (Telmi). Dissolution performance was compared with that of the corresponding reference products. **Methods**: A regulatory-focused, multimedia dissolution strategy was designed to evaluate the release characteristics of all three active pharmaceutical ingredients under conditions reflecting gastrointestinal pH variability. Dissolution testing was conducted in acid buffer (pH 1.2), acetate buffer (pH 4.5), phosphate buffer (pH 6.5) containing 0.5% Tween 80 for Efo and Chlor, and phosphate buffer (pH 7.5) for Telmi. The study was performed for two FDC strengths (Efo + Chlor + Telmi: 40 mg + 6.25 mg + 40 mg and 40 mg + 12.5 mg + 40 mg) to ensure consistency of release performance across dosage variants. **Results**: Efo showed negligible release in pH 1.2 and 4.5 media due to poor solubility, whereas Chlor demonstrated rapid and complete dissolution across all conditions. Telmi exhibited marked pH-dependent solubility; incorporation of alkalizers significantly enhanced its release, achieving nearly complete dissolution in phosphate buffer. Model-independent analysis using f_1 and f_2 factors confirmed similarity between test and reference formulations for all APIs in the selected media. Dissolution efficiency, mean dissolution time, and mean dissolution rate were comparable. Kinetic modeling indicated Korsmeyer–Peppas release for Efo and Chlor, and Weibull release behavior for Telmi in both formulations. **Conclusion**: The findings indicate similar dissolution characteristics and underlying release kinetics, confirming pharmaceutical equivalence of the test FDC tablet with the reference products and establishing its appropriateness for regulatory evaluation and routine quality control.

Keywords: Fixed dose combinations, multimedia dissolution, similarity and dissimilarity factor, efonidipine hydrochloride ethanolate, chlorthalidone, telmisartan

INTRODUCTION

Fixed-dose combinations (FDCs) of antihypertensives, such as angiotensin-converting enzyme (ACE) inhibitors combined with calcium channel blockers and/or diuretics, are necessary to achieve optimal blood pressure control in most patients, as monotherapy is not effective in all cases. The American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines advocate for early initiation of FDCs in patients with grade 2 and 3 hypertension or higher risk, which can lead to better cardiovascular outcomes, such as reduced rates of cerebrovascular and heart failure events (*1–3*).

For solid oral dosage formulations like tablets and capsules to have consistent bioavailability, therapeutic efficacy, and safety, dissolution testing is essential as it mimics drug release in the gastrointestinal tract. According to the United States Food and Drug Administration (FDA) and United States Pharmacopeia (USP), the dissolution test is used as a quality control tool during development to monitor batch-to-batch uniformity, stability, and post-approval modifications; improve formulations; forecast in vivo performance using in vivo-in vitro correlation (IVIVC) models (particularly for Biopharmaceutics Classification System (BCS) class II/IV medications); and minimize the need for expensive bioequivalence studies by creating surrogate measures for absorption rates (*4–7*).

An essential part of the development and regulatory review of FDC tablets is the comparative dissolution assessment of the test and reference products. Establishing similarity during the creation of generic products guarantees pharmacological equivalency and offers a preliminary indication of possible in vivo bioequivalence. This helps to guide formulation improvement and minimizes the amount of clinical testing necessary. Dissolution comparison is required by regulatory agencies (e.g., FDA EMA, WHO) for post-approval modifications, such as changes to the manufacturing site, equipment, batch size, or excipient supply, to ensure that these changes do not affect the release properties of the active pharmaceutical ingredient(s) (API) within the FDC. Comparative dissolution testing across biorelevant and compendial media is crucial from the standpoint of regulatory submission to show that the test product satisfies the performance and quality requirements of the Reference Listed Drug. To approve generic FDC formulations, this guarantees method appropriateness, supports the Quality Target Product Profile (QTPP), and offers proof of consistent in vitro performance (*8–10*).

To verify bioequivalence, generic products must be compared to branded (reference) products using in vitro dissolution experiments. The data are evaluated using metrics like difference factor (f_1, 0–15) and similarity factor (f_2, 50–100) and kinetic release models to study the potential impact of formulation variations in excipients or manufacturing that may alter absorption. Dissolution testing prevents therapeutic failures, supports market approval, and safeguards public health by verifying the quality of generic medicines (*11–13*).

In the current study, dissolution profiles were compared for two strengths (low and high) of a bilayer FDC test tablet containing efonidipine hydrochloride ethanolate (Efo), chlorthalidone (Chlor), and telmisartan (Telmi) (low: 40 mg Efo + 6.25 mg Chlor + 40 mg Telmi; high: 40 mg Efo + 12.5 mg Chlo + 40 mg Telmi) with their respective reference products using a model-independent and model-dependent approach and standard dissolution parameters.

METHODS

Materials

Efo, Chlor, and Telmi were procured from Emcure Pharmaceuticals Ltd. (Pune, India), Ipca Laboratories Ltd. (Mumbai, India), and Vasudha Pharma (Hyderabad, India), respectively. Reference drug products used for Efo, Chlor, and Telmi were Landel 40 mg (Shionogi & Co., Japan), CTD 6.25 mg and 12.5 mg (Ipca Laboratories), and Micardis 40 mg (Boehringer Ingelheim, France), respectively. Details are presented in Table 1.

Table 1. Details for Efonidipine, Chlorthalidone, and Telmisartan Products

Generic Name	Brand Name	Batch No.	Exp. Date	Manufacturer
Efonidipine Tablets	Landel 40 mg	507B08	Aug 2014	ZERIA Pharmaceutical Co. Ltd, Japan
Chlorthalidone Tablets IP	CTD 6.25 mg CTD 12.5 mg	EKA084005AS DWL104006AS	May 2026 Jun 2027	IPCA Laboratories Ltd.
Telmisartan Tablets	MICARDIS 40 mg	F74721	Feb 2028	Boehringer Ingelheim
Efonidipine, Chlorthalidone & Telmisartan Tablets (40 mg + 6.25 mg + 40 mg)	NA	FD/ECT/08	NA	Poona College of Pharmacy / Zuventus Healthcare Ltd
Efonidipine, Chlorthalidone & Telmisartan Tablets (40 mg + 12.5 mg + 40 mg)	NA	FD/ECT/12	NA	Poona College of Pharmacy / Zuventus Healthcare Ltd

Exp.: expiration; NA: not applicable (self-made test samples).

Development of Bilayer Fixed-Dose Combination (FDC) Tablet

Bilayer tablets were prepared with Efo and Chlor in one layer and Telmi in another layer using a bilayer tablet compression machine (CMB3 D-17/MT, Cadmach, India). The bilayer FDC tablets were developed in low strength (Efo 40 mg + Chlor 6.25 mg + Telmi 40 mg) and high strength (Efo 40 mg +Chlor 12.5 mg +Telmi 40 mg).

Efonidipine Hydrochloride Ethanolate (Efo)

A solid dispersion method was adopted to prepare Efo granules by using methanol, methylene chloride, hydroxypropyl methylcellulose acetate succinate, dibasic calcium phosphate anhydrous, microcrystalline cellulose (PH101), and crospovidone (polyplasdone XL 10) to improve solubility in an alkaline medium.

Chlorthalidone (Chlor)

A simple wet granulation method was used to prepare Chlor granules using micronized Chlor (5-10µ), microcrystalline cellulose (PH101), sodium starch glycolate, povidone IP (PVP K-30), and water.

Telmisartan (Telmi)

A solid dispersion method was used to prepare Telmi granules using sodium hydroxide (pellets), meglumine, povidone (PVP K-25), mannitol (Pearlitol 50C and SD 200), talc, and magnesium stearate to enhance solubility and dissolution.

Equipment Performance Qualification

The dissolution test apparatus (Electrolab, USP type 2) was calibrated using standard Prednisone tablet (Lot no. R083A0) in accordance with USP guidelines against set parameters for bench top levelness (limit < 1.0°) and bench plate inclination (< 0.5°); time check (limit ±

2.0% of set time), vessel temperature (37.0 ± 0.5 °C) and verticality (90.0 ± 0.5°); shaft verticality (90.0 ± 0.5°), centering (< 2.0 mm), and depth (25.0 ± 2.0 mm); rpm check (< 2.0 mm, 20-300 rpm); wobble (< 1.0 mm); and volume measurement-syringe system volume accuracy (10.0 ± 0.5 mL) (*14*, *15*). The percentage drug release obtained from all six vessels was within the acceptable limits specified by pharmacopeial standards. The %RSD for drug release was found to be less than 5.0% (1.85%), indicating good reproducibility of the dissolution system. Temperature variation across vessels was within ± 0.5 °C (37.1-37.2 °C), and no significant deviation in rpm or other mechanical parameters was observed. Thus, the dissolution system met the required performance criteria and was suitable for routine dissolution testing.

Through systematic analysis of critical parameters such as pump flow rate accuracy, column oven and sample cooler temperature, gradient composition accuracy, detector response, wavelength accuracy, and auto-injector performance, the performance of the RP-HPLC system was qualified. Pump flow rates studied between 0.5 and 2.0 mL/min were determined to be within ± 2% of predetermined set values. Column oven temperatures (20, 30, and 60 °C) and sample cooler temperatures (5 and 15 °C) were within ± 2% and ± 3% of acceptable limits, respectively. Gradient proportioning valve (GPV) values of 9.42% and 10.14% were obtained with 10% gradient composition accuracy, falling within the permissible range (9.0–11.0%). Detector precision was found to be high, with a %RSD of 0.10, while the detector response exhibited excellent linearity, as indicated by a correlation coefficient of 1.000. Wavelength accuracy was verified at 206 and 273 nm, with observed values of falling within ± 2 nm of the set wavelengths. The auto-injector demonstrated precise delivery of the set injection volume (20.0 µL), with a highly linear response (R = 1.000) and absence of carryover. All evaluated parameters complied with the established acceptance criteria, confirming suitability of the RP-HPLC system for routine analytical applications.

Selection of Dissolution Media

The multimedia dissolution study for FDC tablets is a regulatory-standard in vitro test that evaluates the drug release profiles of all APIs simultaneously across a range of physiological conditions. This approach is used for quality control, assessing bioequivalence for post-approval changes or biowaivers, and to construct a predictive IVIVC. For both strengths of FDC tablets, multimedia dissolution was performed in three pH conditions, i.e., pH 1.2 acid buffer, pH 4.5 acetate buffer, and pH 6.5 phosphate buffer with 0.5% Tween 80 (for Efo and Chlor) or pH 7.5 phosphate buffer (for Telmi). For Efo and Chlor, phosphate buffer (pH 6.5) containing 0.5% Tween 80 was selected as the optimized dissolution medium. Both drugs exhibit limited aqueous solubility, with Efo being highly lipophilic and prone to dissolution rate limitations under nonsurfactant conditions. Tween 80 was used to enhance wettability, stop precipitation, and guarantee sink conditions were maintained. The dissolution results for Efo and Chlor in slightly acidic-to-neutral pH of 6.5 with 0.5% Tween 80 were reproducible with low variability. On the other hand, the USP's compendial medium, phosphate buffer (pH 7.5) was used to assess Telmi dissolution. This assured proper ionization, improved Telmi solubility, and conformity to regulatory requirements (*16*).

The variations in solubility profiles, pKa values, and release properties of the multiple APIs provided scientific justification for the use of different dissolution media in the bilayer FDC. This strategy supported thorough formulation review and quality control assessment by guaranteeing reproducible dissolution profiles for Efo and Chlor while preserving compendial conformance for Telmi (*14*).

Validation of Dissolution Method

The developed dissolution method was validated in accordance with ICH guidelines for analytical method validation (*17*, *18*). This included assessment for specificity and linearity of the analytical method, as well as accuracy, precision, robustness, filter compatibility, and stability studies.

Dissolution Test and Analysis

Multimedia dissolution testing was performed using an Electrolab dissolution apparatus (USP apparatus 2) with 900 mL of dissolution media. For Efo and Chlor, pH 1.2 hydrochloride buffer, pH 4.5 acetate buffer, and pH 6.5 phosphate buffer with 0.5% Tween 80 were used at 100 rpm; whereas for Telmi, pH 1.2 hydrochloride buffer, pH 4.5 acetate buffer, and pH 7.5 phosphate buffer were used at 75 rpm. Samples (5 mL) were withdrawn at 15, 30, 45, and 60 min and were filtered using a 0.45-µm nylon filter. The initial dissolution volume was maintained by replacing the withdrawn sample with an equal volume of fresh dissolution medium at each time point. The drug concentration was estimated by a validated gradient reverse phase high-performance liquid chromatography (RP-HPLC) method.

To compare the dissolution profiles of the bilayer tablet formulation components with the respective reference product for each API, the f_1 and f_2 values, dissolution efficiency (DE), mean dissolution time (MDT), and mean dissolution rate (MDR) were calculated in Microsoft Excel using the obtained data.

Release Kinetics

The dissolution data (percent drug release) were fitted into various release models including zero order, first order, Higuchi diffusion, Korsmeyer-Peppas, Hixon Crowell, and Weibull to calculate various dissolution statistics using DDSolver Excel plugin (Microsoft Excel add-in, version 1). The optimal model was identified based on statistical evaluation, selecting the one exhibiting the highest coefficient of determination (R^2), and the lowest Akaike Information Criterion (AIC) (*19*).

RESULTS AND DISCUSSION

The developed triple combination tablet containing Efo, Chlor, and Telmi is novel as it combines a dual L- and T-type calcium channel blocker, a thiazide-like diuretic, and an angiotensin II receptor blocker, respectively, in a single dosage form, offering complementary and comprehensive blood pressure control. This combination addresses multiple pathophysiological pathways of hypertension, mitigates individual drug-related adverse effects, reduces pill burden, and represents a therapeutic and formulation advancement beyond existing dual antihypertensive combinations. For the development of this FDC, the individual API was processed separately to address the solubility issues of each drug, as Efo, Chlor, and Telmi belong to BCS class II, IV, and II, respectively (*20, 21*).

Validation of Dissolution Method

The analytical method demonstrated adequate specificity, as no interference was observed from excipients or dissolution media at the retention times of the analytes.

Linearity was established over the concentration range of 0.31-0.94 µg/mL for Chlor, 2-60 µg/mL for Efo, and 2-60 µg/mL for Telmi, with $R^2 \geq 0.9998$, indicating excellent linear relationships.

Recovery studies at 5%, 50%, 100%, and 150% concentration levels were used to assess the accuracy of method. The results demonstrated that recoveries for Efo, Chlor, and Telmi were in the range of 96.41-103.38%, 99.00-102.5%, and 97.38-102.35%, respectively. Repeatability and intermediate precision were assessed; %RSD values below 5.0% indicated acceptable variability. Repeatability showed %RSD values of 0.55% (Efo), 1.92% (Chlor), and 3.15% (Telmi), while intermediate precision (n = 12) demonstrated absolute differences of 3.41%, 0.45%, and 3.10%, respectively.

Robustness of the method was verified by deliberate variations in parameters such as paddle speed (± 4%), dissolution volume (± 10mL), and dissolution media temperature (± 0.5°C), which did not significantly affect the dissolution profile. Furthermore, a 0.45-µm nylon filter and Whatman No. 40 filter paper were found to be compatible with formulation excipients. Filter compatibility studies confirmed no significant adsorption of drug onto the filter media.

The standard and sample solutions were found to be stable for up to 36 hours under specified conditions.

Overall, the method was found to be reliable, reproducible, and suitable for routine dissolution testing of the developed formulation.

Comparison of Multimedia Dissolution Profiles

Dissolution profiles are presented in Figures 1 and 2. The similarity and dissimilarity for all three drugs in various buffers for both strengths are reported in Table 2.

Efonidipine Hydrochloride Ethanolate (Efo)

In pH 1.2 acid buffer, the release of Efo from both the test and reference product was negligible (Fig. 1a). Similarly, Efo was not released in pH 4.5 acetate buffer (Fig. 1b). This can be attributed to insolubility of Efo in acidic media (experimental solubility - 0.001 mg/mL). Efo has absorption window in the upper part of intestinal tract, so it was formulated as a solid dispersion using hypromellose acetate succinate (HPMCAS), which has pH-dependent solubility (soluble at pH ≥ 6.5), leading to little or no drug release in both pH 1.2 acid and pH 4.5 acetate buffers. Because no dissolution was observed from in pH 1.2 acid or pH 4.5 acetate buffers, f_1 and f_2 analysis was not done.

In pH 6.5 phosphate buffer with 0.5% Tween 80, more than 90% Efo release was achieved for the test and reference product (Fig. 1c). A slight, non-significant difference in the overall dissolution curve was recorded (f_1 = 8.19 and f_2 = 58.47) (Table 2). At pH 6.5 phosphate buffer, HPMCAS undergoes ionization of succinoyl groups, resulting in polymer swelling and dissolution. This facilitates disintegration of the solid dispersion matrix and release of amorphous dispersed Efo. Additionally, the addition of 0.5% Tween 80, a nonionic surfactant, improves drug wetting and micellar solubilization and prevents drug precipitation, all of which aid in dissolving. In accordance with intestinal pH-triggered drug release behavior, the observed dissolving pattern represents a combined effect of polymer enteric solubility threshold, drug physicochemical features, and surfactant-mediated solubilization.

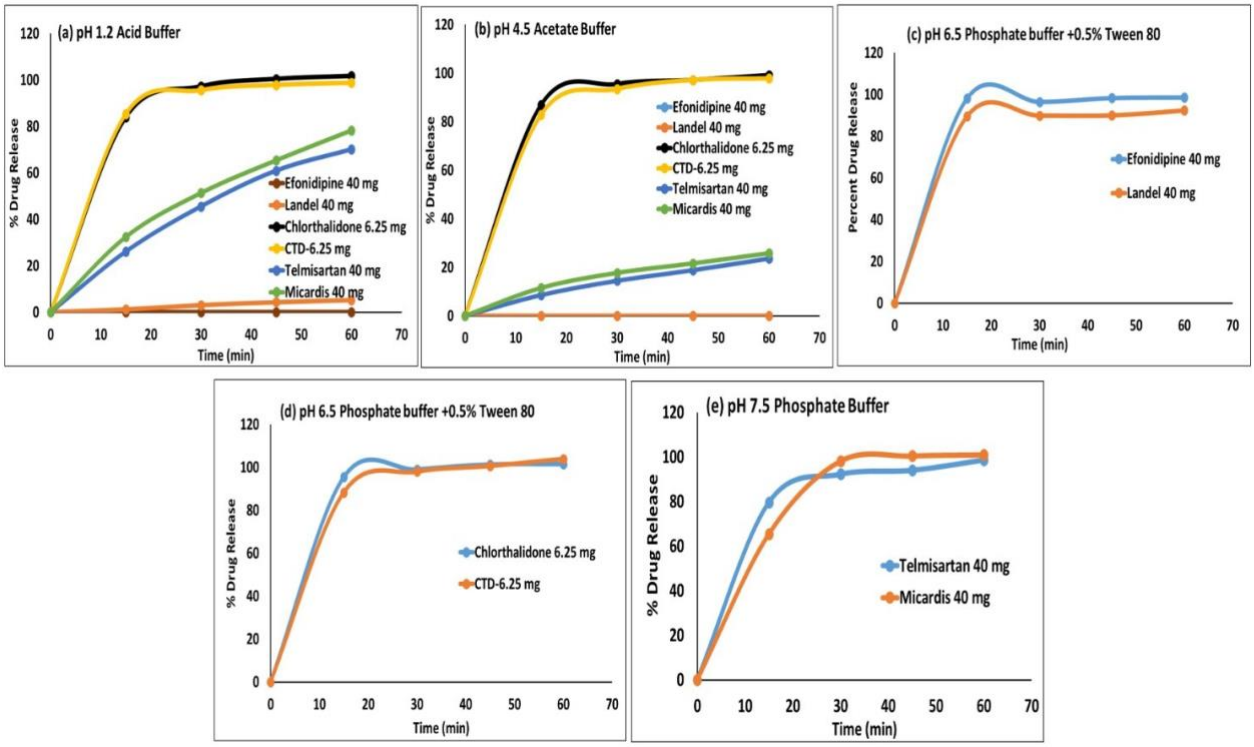

Figure 1. Comparison of multimedia dissolution profiles of low-strength FDC bilayer tablets containing efonidipine (40 mg), chlorthalidone (6.25 mg) and telmisartan (40 mg) versus Landel (40 mg), CTD (6.25 mg), and Micardis (40 mg). Dissolution media: (a) pH 1.2 acid buffer; (b) pH 4.5 acetate buffer; (c and d) pH 6.5 phosphate buffer + 0.5% Tween 80; (e) pH 7.5 phosphate buffer. FDC: fixed-dose combination.

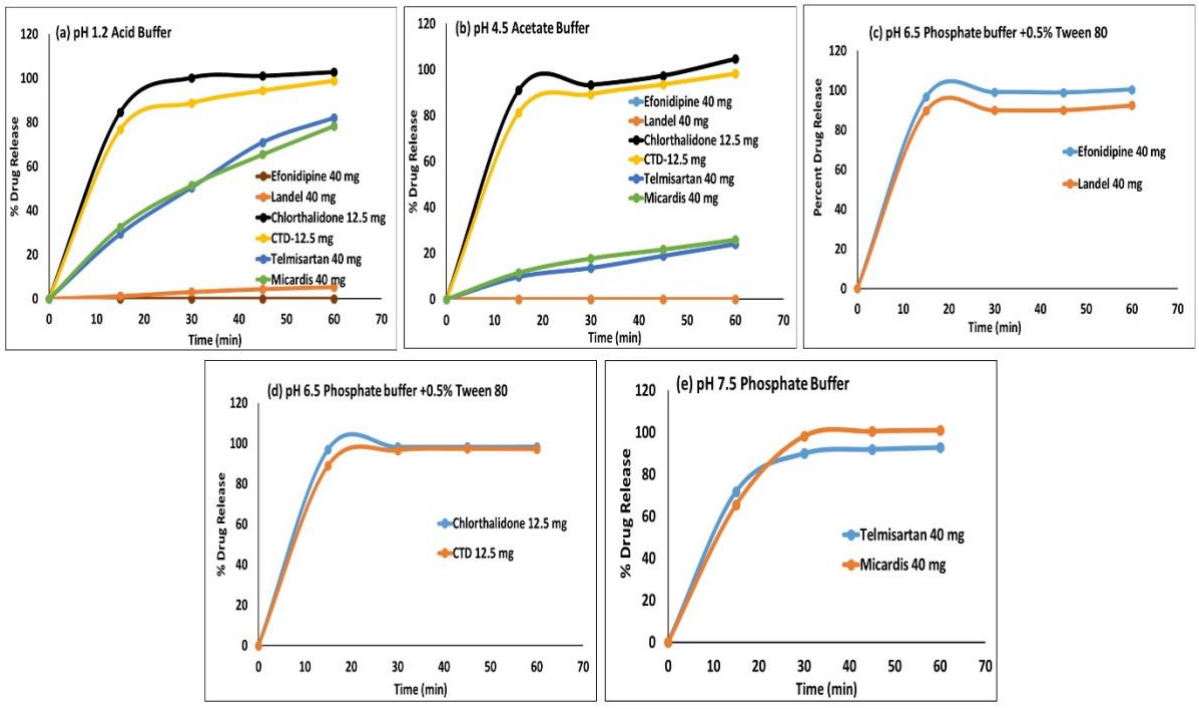

Figure 2. Comparison of multimedia dissolution profiles of high-strength FDC bilayer tablets containing efonidipine (40 mg), chlorthalidone (12.5 mg), and telmisartan (40 mg) versus Landel (40 mg), CTD (12.5 mg), and Micardis (40 mg), respectively.Dissolution media: (a) pH 1.2 acid buffer; (b) pH 4.5 acetate buffer; (c and d) pH 6.5 phosphate buffer + 0.5% Tween 80; (e) pH 7.5 phosphate buffer. FDC: fixed-dose combination.

Table 2. Dissimilarity (f_1) and Similarity (f_2) Factors for Test Products Compared to Reference Products

Dissolution Medium	Efo		Chlor		Telmi	
	f_1	f_2	f_1	f_2	f_1	f_2
Low Strength (40 mg Efo + 6.25 mg Chlor + 40 mg Telmi)						
pH 1.2 Acid buffer	*	*	1.50	82.49	10.93	59.54
pH 4.5 Acetate buffer	*	*	1.99	81.42	14.44	76.34
pH 6.5 Phosphate buffer + 0.5% Tween 80	8.19	58.47	1.66	72.39	*	*
pH 7.5 Phosphate buffer	*	*	*	*	0.005	53.64
High Strength (40 mg Efo + 12.5 mg Chlor + 40 mg Telmi)						
pH 1.2 Acid buffer	*	*	8.28	57.31	2.24	71.11
pH 4.5 Acetate buffer	*	*	6.72	61.36	13.79	76.28
pH 6.5 Phosphate buffer + 0.5% Tween 80	9.13	56.25	3.10	70.65	NA	NA
pH 7.5 Phosphate buffer	NA	NA	NA	NA	4.47	56.41

**As drug release was negligible, similarity and dissimilarity factors were not calculated.*
Efo: efonidipine hydrochloride ethanolate; Chlo: chlorthalidone; Telmi: telmisartan; NA: not applicable.

Chlorthalidone (Chlor)

As depicted in Figure 1 (a, b, and d), Chlor release was more than 95% for both the test FDC tablet and reference (CTD 6.25 mg) in all the three pH buffers. A similar release profile was observed for the high-strength dose with 12.5 mg Chlor (Fig. 2). Chlor is categorized as a BCS class IV drug, with inherently low solubility and permeability. The enhanced dissolution from the FDC tablet is likely attributable to the use of micronized Chlor (particle size ~5–10 µm) in the formulation, where particle size reduction increases surface area, improves wettability, and consequently facilitates faster dissolution across different pH conditions.

As reported in Table 2, the dissolution curve for Chlor release all pH buffers was found to be similar to the reference product, CTD 6.25mg (f_2 = 82.49, 81.42, and 72.39, respectively).

Telmisartan (Telmi)

In pH 1.2 acid buffer, Telmi release was approximately 70% from FDC tablet, whereas 78% drug was released from reference product (Micardis) (Fig. 1a); however, f_2 was 59 (Table 2), indicating no significant difference in the drug release profile. In pH 4.5 acetate buffer, approximately 24% and 26% Telmi was released from the test and reference products, respectively (Fig. 1b), and f_2 was 76.

The lower dissolution of Telmi solid dispersion in pH 4.5 acetate buffer compared to pH 1.2 acid buffer is mainly due to its pH-dependent ionization behavior. Telmi is a weakly acidic, highly lipophilic drug (pKa ~3.5–4.5); at pH 1.2, it remains predominantly in an ionized salt form with higher ionic strength, improved wettability, and better solvation, resulting in enhanced apparent solubility and dissolution. In contrast, pH 4.5 lies close to its pKa, where partial ionization leads to salt-to-free acid conversion (pH-induced salt disproportionation),

forming the poorly soluble, highly lipophilic unionized acid that tends to precipitate. The weaker acetate buffer and lower ionic strength further reduce solvation efficiency, promoting aggregation and precipitation, thereby decreasing dissolution at pH 4.5 (*22*).

Pure Telmi has pH-dependent solubility, and it did not show any solubility in pH 7.5 phosphate buffer. To overcome this solubility limitation, use of alkalizers to change the microenvironment pH was used, which resulted in solubility enhancement by 148-times. After 60 minutes of dissolution, approximately 100% drug release was achieved from the test and reference products (Fig. 1e), with an f_2 value of 53.64, thereby demonstrating similarity.

Other Dissolution Parameters

Furthermore, dissolution parameters DE, MDT and MDR were evaluated using the drug release data obtained in phosphate buffer, the USP-recommended dissolution medium. There were no differences in these parameters when the test and reference products were compared.

A generic formulation can be deemed replaceable with the innovator product if the difference in DE values remains within ± 10% (*23*). Although no regulatory acceptance limits are defined for MDT and MDR, comparable values (within approximately ± 10–15%) between test and reference formulations, along with acceptable f_2 values, indicate similarity in dissolution behavior. As reported in Table 3, all parameters were within the acceptable limit except MDT values for test and reference Chlor (8.79 vs 11.09 min). However, the f_2 value for Chlor versus the reference was 72.39, indicating similarity of the dissolution profiles.

Table 3. Dissolution Parameters for Test and Reference Products

Dose Strength	Parameter	Efo*		Chlor*		Telmi#	
		Test	Reference	Test	Reference	Test	Reference
Low Strength (40 mg Efo + 6.25 mg Chlor + 40 mg Telmi)	DE (%)	86.79	85.43	85.35	81.51	79.90	77.89
	MDT (min)	7.92	8.74	8.79	11.09	12.06	13.26
	MDR (%/min)	2.61	2.40	2.59	2.47	2.27	2.05
High Strength (40 mg Efo + 12.5 mg Chlor + 40 mg	DE (%)	85.86	85.43	87.10	85.29	80.90	77.89
	MDT (min)	8.48	8.74	7.74	8.82	11.46	13.26
	MDR (%/min)	2.60	2.40	2.60	2.44	2.09	2.05

**Dissolution medium: pH 6.5 phosphate buffer +0.5% Tween 80.*
#Dissolution medium: pH 7.5 phosphate buffer.
Efo: efonidipine hydrochloride ethanolate; Chlo: chlorthalidone; Telmi: telmisartan; DE: dissolution efficiency; MDT: mean dissolution time; MDR: mean dissolution rate.

As the obtained dissolution data were not complex and variability was low (< 20%), f_2 bootstrap and multivariate statistical distance (MSD) assessments were not performed.

Release Kinetics

As recommended by the FDA, model-dependent approaches, wherein dissolution data are fitted to kinetic models to evaluate similarity between profiles, are particularly useful for handling highly variable dissolution data (e.g., % coefficient of variation > 20% at early time points and > 10% at later points), thereby providing a more robust assessment alongside model-independent approaches (*13*). Although variation in the obtained dissolution data of was insignificant, release kinetics were determined using model-dependent approach to

identify the effect of formulation differences on the release mechanism for the test and reference products.

As shown in Table 4, the FDC test tablets (low and high strength) followed the same release kinetic model as reference product. Based on R^2 and AIC, Efo and Chlor release followed the Korsmeyer-Peppas model, whereas Telmi release followed the Weibull model. This observation indicates that the dissolution behavior of the test and reference products is comparable, despite differences in the formulation composition between the FDC tablet and the individual reference APIs.

Table 4. Dissolution Data Kinetic Model Comparison for Test and Reference Products

Kinetic Model	Statistic	Efo*		Chlor*		Telmi#	
		Test	Reference	Test	Reference	Test	Reference
Low Strength (40 mg Efo + 6.25 mg Chlor + 40 mg Telmi)							
Zero	R^2	0.7125	0.7233	0.7424	0.7897	0.8090	0.8620
	k	2.179	2.02	2.23	2.22	2.09	2.15
	AIC	45.74	44.79	45.43	44.45	43.38	42.09
First	R^2	0.9996	0.9935	0.9998	0.9992	0.9985	0.9957
	k	0.263	0.135	0.206	0.143	0.10	0.081
	AIC	16.00	29.17	9.86	16.10	19.76	24.17
Higuchi Diffusion	R^2	0.8820	0.8892	0.903	0.9327	0.944	0.9675
	k	15.55	14.40	15.86	15.73	14.74	14.98
	AIC	40.21	39.13	39.44	37.60	36.06	33.48
Korsmeyer-Peppas	R^2	0.9998	0.9998	1	0.9998	0.9993	0.9873
	k	96.44	85.02	84.35	65.37	54.50	33.81
	AIC	8.54	7.86	2.82	10.02	15.62	30.24
Hixon Crowell	R^2	0.9569	0.9597	0.9702	0.9865	0.9909	0.9999
	k	0.024	0.023	0.025	0.024	0.023	0.021
	AIC	34.72	34.26	33.20	29.14	27.39	15.98
Weibull	R^2	0.9998	0.9998	0.9998	0.9992	0.9997	1
	β	0.044	0.069	0.795	0.973	0.498	1.92
	AIC	10.60	10.06	13.68	20.09	13.44	6.61
High Strength (40 mg Efo + 12.5 mg Chlor + 40 mg Telmi)							
Zero	R^2	0.7267	0.7233	0.7143	0.7515	0.819	0.8620
	k	2.20	2.02	2.18	2.14	1.99	2.15
	AIC	45.62	44.79	45.72	44.84	42.66	42.09
First	R^2	0.9999	0.9935	0.9998	0.9960	0.9968	0.9957
	k	0.23	0.135	0.23	0.14	0.079	0.08
	AIC	5.34	29.17	12.76	16.68	23.49	24.17
Higuchi Diffusion	R^2	0.8923	0.8892	0.8841	0.9097	0.9499	0.9675
	k	15.72	14.40	15.57	15.20	14.04	14.98
	AIC	39.87	39.13	40.13	38.67	35.03	33.48
Korsmeyer-Peppas	R^2	1	0.9998	1	0.9949	0.9963	0.9873
	k	90.48	85.01	94.69	0.064	46.67	33.81
	AIC	2.65	7.86	-5.20	14.99	23.24	30.24
Hixon Crowell	R^2	0.9650	0.9597	0.9602	0.9765	0.9925	0.999
	k	0.025	0.023	0.024	0.024	0.02	0.021
	AIC	33.85	34.26	4.35	31.48	27.92	15.98
Weibull	R^2	0.9999	0.9998	1	1	1	1
	k	0.425	0.069	0.022	0.056	0.123	1.92
	AIC	5.10	10.06	-35.97	-6.66	-17.07	6.61

**Dissolution medium: pH 6.5 Phosphate buffer +0.5% Tween 80; # Dissolution medium: pH 7.5 Phosphate buffer. AIC: Akaike Information Criterion; Efo: efonidipine hydrochloride ethanolate; Chlo: chlorthalidone; Telmi: telmisartan.*

CONCLUSION

The results indicate that the optimized bilayer FDC tablets exhibit reliable and reproducible dissolution profiles under physiologically relevant conditions. Comparable release patterns, kinetic modeling outcomes, and calculated dissolution parameters demonstrate alignment of the test formulation with the reference products, supporting pharmaceutical equivalence. These outcomes further establish the method's applicability for routine quality control, evaluation of post-approval formulation changes, and potential use in biowaiver considerations or IVIVC development.

DISCLOSURES

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