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RESEARCH ARTICLE

Pharmaceutical Design, Formulation Optimization, and In Vitro Performance Profiling of Generic Lymecycline Capsules Using Validated Analytical Methods

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Abstract: This study documents the stepwise development and evaluation of a generic Lymecycline 408 mg hard gelatin capsule manufactured locally in Pakistan. The formulation process began with the selection of suitable pharmacopeial excipients after conducting accelerated compatibility testing to ensure that no undesirable physical or chemical interactions occurred with the active ingredient. Based on these preliminary investigations, a stable capsule composition was finalized. The finished capsules were evaluated according to British Pharmacopoeia requirements. All tested quality attributes, including assay, dissolution behavior, content uniformity, and moisture content, were found to comply with the specified limits. These results confirmed the consistency and integrity of the developed dosage form. Quantitative analysis of Lymecycline was carried out using a high-performance liquid chromatography method that was validated prior to routine application. During validation, parameters such as specificity, precision under repeat and intermediate conditions, accuracy through recovery assessment, robustness against minor variations, and system suitability were carefully examined. The method demonstrated reliable and reproducible performance in line with internationally accepted regulatory standards. To assess comparative in-vitro performance, dissolution testing was performed using the USP paddle method in media representing gastric and intestinal pH conditions (pH 1.2, 4.5, and 6.8). In all cases, more than 85% of the drug was released within one hour. Statistical comparison with the reference product, Tetralysal® 300 mg, showed acceptable similarity and difference factor values, indicating comparable release profiles. Overall, the data support that the developed formulation performs equivalently to the reference product and may be considered suitable for local production and further regulatory processing.

Keywords: dissolution studies, hard gelatin capsule, HPLC method validation, Lymecycline, pharmaceutical equivalence

1 Introduction

Lymecycline is a semisynthetic derivative of the tetracycline family having chemical name is Lymecycline is N6-4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a- pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenylcarbonyl- aminomethyl-L-lysine. Compendial name is Lymecycline with molecular formula is $C_{29}H_{38}N_4O_{10}$and molecular weight is 602.63, synthesized through the chemical modification of tetracycline by coupling it with L-lysine and formaldehyde, which enhances its solubility and bioavailability [1–3]. Classified as a second-generation tetracycline, Lymecycline was developed to overcome the limitations of earlier agents like tetracycline and chlortetracycline, particularly in terms of absorption, tissue distribution, and side effect profile [3]. The second-generation tetracyclines, including doxycycline and minocycline, were introduced to provide broader clinical utility and improve tolerability [4].

The history of tetracyclines begins with chlortetracycline (aureomycin), discovered in the late 1940s from *Streptomyces Aureofaciens*, marking the advent of a new era in antimicrobial therapy [5]. Tetracyclines quickly gained prominence due to their ability to inhibit a wide range of pathogens. Over time, structural modifications led to newer agents like doxycycline, minocycline, and Lymecycline, each with improved pharmacokinetic and pharmacodynamic

characteristics [6]. These drugs are now used not only for infectious diseases but also for dermatological applications, such as acne and rosacea, due to their dual antimicrobial and anti-inflammatory actions [7].

Mechanistically, Lymecycline like other tetracyclines acts as a bacteriostatic agent by inhibiting bacterial protein synthesis. It binds reversibly to the 30S ribosomal subunit, thereby preventing the attachment of aminoacyl-tRNA to the A site of the ribosome, effectively halting peptide elongation. This interruption disrupts bacterial replication and growth, accounting for its efficacy against a broad spectrum of gram-positive and gram-negative organisms [8].

Lymecycline demonstrates activity against several clinically relevant pathogens, including *Cutibacterium acnes*, *Chlamydia trachomatis*, *Mycoplasma pneumoniae*, and *Rickettsia* species [9]. This broad antimicrobial spectrum underpins its use in managing conditions like respiratory infections, sexually transmitted infections, and dermatologic disorders such as acne vulgaris [10].

One of the distinctive advantages of Lymecycline lies in its pharmacokinetics. It exhibits higher water solubility compared to its parent compound, resulting in more efficient oral absorption and greater bioavailability [11]. Once ingested, Lymecycline undergoes rapid hydrolysis in the gastrointestinal tract to release tetracycline, which is the pharmacologically active moiety, confirming its role as a prodrug [12]. Plasma concentration studies reveal that only tetracycline is present systemically after oral administration of Lymecycline, supporting this metabolic transformation [13].

Additionally, Lymecycline provides better tissue penetration and has a longer half-life than older tetracyclines, which allows for once-daily or twice-daily dosing and improved patient compliance [14]. Gastrointestinal side effects such as nausea and abdominal discomfort, commonly observed with tetracycline, appear to occur less frequently with Lymecycline, making it more suitable for long-term use [15]. A primary therapeutic application of Lymecycline is in the treatment of moderate to moderately severe acne vulgaris. Acne pathogenesis involves follicular occlusion, sebum overproduction, *C. acnes* colonization, and inflammation [16]. Lymecycline helps reduce *C. acnes* levels and exerts anti-inflammatory effects by inhibiting neutrophil chemotaxis and the release of inflammatory cytokines [17]. This dual action enhances its effectiveness in inflammatory acne, especially when topical treatments are insufficient [18].

Beyond acne, Lymecycline has been explored in the management of hidradenitis suppurativa (HS) a chronic inflammatory skin disorder characterized by recurrent nodules, abscesses, and sinus tracts. Tetracyclines, including Lymecycline, are among the first-line systemic treatments recommended in European S1 guidelines for mild to moderate HS [19]. Their efficacy is attributed to both antimicrobial effects and modulation of the immune response, although high-quality randomized trials are still needed to strengthen the evidence base [20].

Despite these benefits, Lymecycline, like all tetracyclines, carries a risk of adverse effects, notably photosensitivity reactions. Phototoxicity arises when the drug absorbs ultraviolet light, resulting in oxidative damage to the skin. While rare, this reaction necessitates preventive counseling for patients on sun exposure and photoprotection measures. Interestingly, Lymecycline appears to have a lower incidence of such reactions compared to earlier tetracyclines, although comprehensive epidemiological data are still evolving. In conclusion, Lymecycline exemplifies the evolution of tetracycline antibiotics into more patient-friendly formulations with enhanced therapeutic profiles. It combines the antimicrobial spectrum and anti-inflammatory properties of its class with improved pharmacokinetics, reduced side effects, and better patient adherence. These attributes make it an excellent candidate for managing chronic dermatological conditions like acne vulgaris and HS. Future studies may explore its potential in resistant infections and inflammatory disorders. The Chemical structure of Lymecycline is shown in Figure 1.

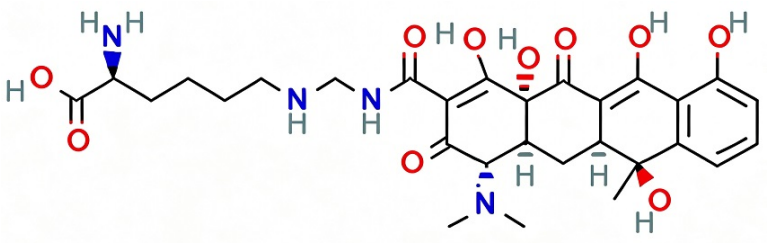

Figure 1 Chemical structure of Lymecycline (National Center for Biotechnology Information (2025). PubChem Compound Summary for Lymecycline. from https://pubchem.ncbi.nlm.nih.gov/compound/Lymecycline)

1.1 Problem Statement

Despite the established clinical efficacy of Lymecycline in managing moderate-to-severe acne and other dermatological infections, the accessibility of this essential antibiotic in developing healthcare markets like Pakistan remains severely limited. Currently, the market is characterized by a high reliance on expensive innovator brands (e.g., Tetralysal®), which imposes a significant socio-economic burden on patients and often leads to sub-optimal treatment adherence. Furthermore, the absence of a locally manufactured, pharmaceutically equivalent generic version creates a gap in the supply chain and prevents cost-effective therapeutic interventions. There is a critical need to develop a robust, stable, and validated generic formulation that adheres to stringent British Pharmacopoeia (BP) and International Council for Harmonisation (ICH) standards to ensure safety and efficacy comparable to the reference product.

1.2 Relevance of Research

This study holds significant clinical and industrial relevance as it presents the development of the first generic Lymecycline 408 mg capsule in Pakistan. By employing a Quality-by-Design (QbD) approach and rigorous analytical validation, this research:

(1) **Enhances Patient Access:** Provides a cost-effective alternative to the innovator drug, facilitating long-term management of chronic skin conditions.

(2) **Validates Analytical Precision:** Establishes a validated HPLC-UV method for the precise quantification of Lymecycline, ensuring high quality-control standards in local manufacturing.

(3) **Demonstrates In-Vitro Bioequivalence:** Through comparative dissolution profiling and f_1/f_2 factor analysis across multiple pH media, this work provides scientific evidence that the generic formulation is pharmaceutically equivalent to the innovator.

(4) **Promotes Local Manufacturing:** This research supports the pharmaceutical 'indigenization' policy, reducing import dependency and strengthening the local healthcare infrastructure.

2 Methodology

2.1 Materials, instruments and Chemicals

Lymecycline hydrochloride (API) was procured from KOPRAN Pharma. Tetracycline hydrochloride (B.P./Eur. Ph.) reference standard with certified potency was used as the reference. Excipients included magnesium stearate, Aerosil-200, and empty gelatin capsule shells (#0), all obtained from local suppliers. For qualitative and quantitative analyses, the following instruments and reagents were employed: a refrigerator, HPLC system equipped with a stationary phase column (4.6 mm $\times$ 25 cm, 5 μm packing, L-7/C8), UV–Visible spectrophotometer, dissolution apparatus (12-basket), Karl Fischer apparatus, glassware (beakers, pipettes, amber-colored volumetric flasks). Analytical grade reagents included hydrochloric acid, purified water, sodium acetate, glacial acetic acid, monobasic potassium phosphate, sodium hydroxide, phosphoric acid, 2-methyl-2-propanol, dipotassium hydrogen orthophosphate, tetrabutylammonium hydrogen phosphate, sodium edetate, and sodium metabisulfite.

2.2 Product Formulation Development

The formulation development of Lymecycline and API calculation are mentioned in Table 1.

Table 1 Scale up of Lymecycline formulation Development

Ingredient	Function / Role	Composition (%)	Amount per Capsule (mg)
Lymecycline (Potency-Adjusted API)[1]	Active Pharmaceutical Ingredient (API)	98.103%	490.517
Magnesium Stearate[2]	Glidant / Lubricant	1.290%	6.483
Aerosil-200	Glidant / Anti-tack Agent	0.600%	3.000
Empty Gelatin Capsule Shell (Size #0, Pink/White)	Finished Dosage Form Vehicle	–	100.000
Total Weight of Formulation Powder Blend	–	100.000%	500.000 mg
Total Weight of Finished Capsule (with Shell)	–	–	600.000 mg

Note: [1] Lymecycline 408 mg is equivalent to 300 mg of Tetracycline base. Potency adjusted to 100% basis; [2] Magnesium Stearate quantity adjusted to compensate for API potency variations to maintain 500 mg fill weight.

The lymecycline active pharmaceutical ingredient (API) was potency-adjusted to 100% based on the assay value provided by Quality Control, and any quantitative variation resulting from this adjustment was compensated by proportionally reducing the amount of magnesium stearate to maintain formulation balance. The physical appearance of the API was visually examined (Figure 2) to ensure compliance with specified quality attributes. During the final mixing (bulk) stage, all pre-processed intermediates were blended under controlled conditions to achieve a homogeneous powder mixture suitable for encapsulation (Figure 2). The blended material was subsequently filled into hard gelatin capsule shells, representing the intermediate (post-encapsulation) stage, during which in-process evaluation, stabilization monitoring, and quality verification were performed prior to final release (Figure 3). After successful completion of all manufacturing steps, in-process controls, and final quality assurance testing, the finished product—lymecycline 408 mg hard gelatin capsules—was packaged in aluminum–aluminum (Alu–Alu) blister strips to ensure protection against moisture, light, and environmental factors (Figure 4). The reference product, Tetralysal® 300 mg capsules, was documented for comparative evaluation (Figure 5 and 6).

Figure 2 Lymecycline Raw Material (API)

Figure 3 Lymecycline formulation development (at Final Mix/ Bulk stage)

Figure 4 Lymecycline formulation development (at Intermediate/ After encapsulation)

Figure 5 The finished pharmaceutical product of Lymecycline (408 mg hard gelatin capsules) was packaged in Alu-Alu foil to ensure protection from moisture, light, and environmental factors.

Figure 6 Reference Product (Tetralysal 300mg) Packed in Aluminum Foil Strip.

2.3 Analytical method Development (HPLC)

2.3.1 Preparation of Diluted: (10% NaOH)

10.0g of the Sodium hydroxide pellets was taken in 90mL volumetric flasks and diluted up to the mark with water.

2.3.2 Mobile Phase

A mobile phase solution was prepared by dissolving 80.0 g of 2-methyl-2-propanol and 3.5 g of dipotassium hydrogen orthophosphate in a 1000 mL volumetric flask containing 300 mL of water. The pH was adjusted to 8.0 using dilute phosphoric acid. Subsequently, 2.0 g of tetrabutylammonium hydrogen phosphate was dissolved in 200 mL of water, the pH adjusted to 8.0 with dilute sodium hydroxide, and the solution was added to the flask. In a separate step, 0.4 g of sodium edetate was dissolved in 10 mL of water, the pH adjusted to 8.0 with dilute sodium hydroxide, and the solution transferred into the same flask. Finally, the volume was made up to the mark with distilled water and mixed thoroughly.

2.3.3 Chromatographic Conditions

(1) Detector: UV 254 nm

(2) Column: 4.6mm $\times$ 25cm; Packing (L-7/C8) (8μm)

(3) Column Temperature: 40ºC$\pm$1ºC

(4) Flow Rate: 1.2 mL/min

(5) Injection Volume: 20 μL

(6) Retention Time: About 5.6 Mint

2.3.4 Preparation of Sodium Meta-bisulfite: (4% w/v)

An accurately weighed quantity of sodium metabisulfite (4.0 g) was transferred into a 96 mL volumetric flask and diluted to volume with distilled water.

2.3.5 Preparation of 0.05M Hydrochloric Acid

2.2mL Hydrochloric Acid (usually 37%) in 50mL water was taken and diluted up to 500mL with water and mix well.

2.3.6 Reference Solution

An accurately weighed quantity of tetracycline hydrochloride reference standard (325 mg, equivalent to approximately 300 mg of tetracycline) was transferred into a 100 mL volumetric flask containing 5 mL of water. To this, 1 mL of sodium metabisulfite solution was added, and the mixture was allowed to stand in the dark at 20–25 °C for 20–24 hours without stirring. Subsequently, 50 mL of 0.05 M hydrochloric acid was added to dissolve the precipitate, and the volume was made up to 100 mL with distilled water. From this solution, 5 mL was transferred to a 100 mL volumetric flask, diluted to volume with water, and filtered through a 0.45 μm nylon membrane filter.

2.3.7 Sample Solution

The contents of not less than 20 Lymecycline capsules were emptied, and an accurately weighed portion equivalent to 500 mg of Lymecycline (approximately equivalent to 300 mg of tetracycline) was transferred into a 100 mL volumetric flask containing 5 mL of water. To this, 1 mL of sodium metabisulfite solution was added, and the mixture was allowed to stand in the dark at 20–25 °C for 20–24 hours without stirring. Subsequently, 50 mL of 0.05 M hydrochloric acid was added to dissolve the precipitate, and the volume was made up to 100 mL with distilled water. From this solution, 5 mL was transferred into a 100 mL volumetric flask, diluted to volume with water, and filtered through a 0.45 μm nylon membrane filter.

2.3.8 Analysis

Six replicate injections of the standard preparation (filtered through a 0.45 μm syringe filter) and two replicate injections of the sample preparation were separately injected into the chromatograph, and the responses of the major peaks were recorded. The percentage of tetracycline was calculated by comparing the peak responses of the sample solution with those of the standard solution. System suitability was considered acceptable if the tailing factor of the major peak of the analyte in the standard solution was not more than 2.0, the number of theoretical plates was not less than 2000, and the relative standard deviation (RSD) for six replicate injections of the standard preparation did not exceed 1.0%.

$$\%\text{age (Tetracycline)} = \frac{\text{Avg. Area of Sample}}{\text{Avg. Area of Standard}} \times \frac{\text{Dil. of Standard}}{\text{Dil. of Sample}} \times \frac{0.9241}{1} \times \text{Potency W.S}$$

$$\%\text{age of Lymecline} = \%age \text{ of Tetracycline} \times 1.356 = \text{———}\%(\text{as lymecline})$$

Note: This Method is also applicable for Lymecycline Raw Material (API).

2.4 Dissolution (By UV Spectrophotometer)

2.4.1 Preparation of Dissolution medium 0.1M Hydrochloric Acid

51 mL of Hydrochloric Acid (usually 37%) in 1000 mL water was taken, diluted up to 6000mL with water and mixed well.Routine dissolution for the developed capsule was performed using USP Apparatus II (paddle) in 900 mL medium at 37 ± 0.5 °C. Comparative profile testing against Tetralysal® 300 mg used twelve units per product in pH 1.2, acetate buffer pH 4.5, and phosphate buffer pH 6.8. Absorbance was measured at 380 nm after alkaline color development. Mean profiles were compared using difference factor (f1) and similarity factor (f2). Standard deviation and %RSD were retained to improve transparency. A limitation of the available dataset is that early sampling points (e.g., 10, 15, and 30 min) were not captured; therefore, conclusions are based on the recorded 45, 60, and 75 min observations only.

2.4.2 Parameters

Dissolution testing was performed using a USP II (paddle) apparatus at 75 rpm, with 900 mL of 0.1 M hydrochloric acid as the dissolution medium. The test was conducted for 60 minutes at a controlled temperature of 37±0.5°C.

2.4.3 Procedure

The procedure was carried out under protection from light. Each of six dissolution vessels was filled with 900 mL of 0.1 M hydrochloric acid, and the medium was equilibrated to 37 ±

0.5 °C. One capsule containing 408 mg of Lymecycline (equivalent to 300 mg of tetracycline) was transferred into each vessel, and the apparatus was immediately operated for 60 minutes.

2.4.4 Sample Preparation

At the designated sampling time, approximately 20 mL of the reaction mixture was withdrawn and filtered through Whatman filter paper to remove particulate matter. A 5mL aliquot of the filtrate was transferred into a 100 mL volumetric flask, to which 50 mL of deionized water and 5 mL of 5 M sodium hydroxide were added. The solution was then diluted to the mark with deionized water and thoroughly mixed. The absorbance of the resulting solution was measured exactly 6 minutes after the addition of sodium hydroxide.

2.4.5 Standard Preparation

An accurately weighed 0.090 g of Tetracycline Hydrochloride working standard was transferred into a 100 mL volumetric flask. 70 mL of 0.1 M hydrochloric acid was added, and the mixture was dissolved completely using stirring and/or sonication. The solution was then diluted to the 100 mL mark with 0.1 M hydrochloric acid, mixed thoroughly, and filtered through Whatman filter paper to remove any insoluble particles. For absorbance measurement, 2 mL of the filtered solution was transferred into a 100 mL volumetric flask, to which 50 mL of deionized water and 5 mL of 5 M sodium hydroxide were added. The solution was diluted to the mark with deionized water, mixed thoroughly, and the absorbance was measured at the maximum wavelength (λ_{max} = 380 nm) exactly 6 minutes after the addition of sodium hydroxide.

2.4.6 Analysis

The percentage of Lymecycline in the medium was calculated from the measured absorbance and the declared content of Tetracycline Hydrochloride. Each milligram of Tetracycline Hydrochloride was considered equivalent to 0.9241 mg of Tetracycline. The content of Tetracycline obtained was then multiplied by 1.356 to determine the corresponding content of Lymecycline.

$$\%\text{age of Tetracycline} = \frac{\text{Absorbance of Sample}}{\text{Average Absorbance of Standard}} \times \frac{\text{Dil. of Standard} \times 0.9241}{\text{Dilution of Sample}} \times \text{Potency of W.S}$$

$$\%\text{age of Lymecline} = \%\text{age of Tetracycline} \times 1.356 = \text{———}\%(\text{as lymecline})$$

2.5 *In vitro* Study (Comparative Dissolution Profile)

2.5.1 Methodology and Regulatory Requirements for In Vitro Dissolution Profile Comparison

To ensure a robust and legally compliant comparison between the Test and Reference (Comparator) products, the following criteria and regulatory guidelines were strictly implemented:

(1) **Standardized Testing Conditions:** Dissolution evaluations for both the test and comparator products were conducted under identical operational parameters to eliminate experimental variability.

(2) **Sample Size and Apparatus:** For each dissolution profile determination, a minimum of 12 individual units (n = 12) were analyzed using USP Apparatus II (Paddle Method) operated at a standard rotational speed of 100 rpm.

(3) **Sampling Time-Points:** A minimum of three chronological time-points were selected for profiling, ensuring that the sampling intervals were perfectly synchronized between the test and reference formulations.

(4) **Physiological Media Selection:** For this immediate-release oral dosage form, comparative profiling was executed across the complete gastrointestinal physiological pH range, utilizing three distinct media: 0.1M Hydrochloric Acid (pH 1.2), Acetate Buffer (pH 4.5), and Phosphate Buffer (pH 6.8). The detailed preparation methodologies and specific volumes for each medium are compiled in Table 2.

(5) **Mathematical Curve Comparison (f_2 Estimation):** The mean dissolution values at each specified time-point were utilized to calculate the similarity factor (f_2) to assess the mathematical equivalence of the release curves.

(6) **Rapid Dissolution Criteria:** In instances where both the test and reference products achieved greater than 85% active pharmaceutical ingredient (API) release within 15 minutes, the profiles were automatically considered profiles of equivalent behavior, rendering further mathematical calculations redundant.

(7) **Acceptance Range for Equivalency:** For the two formulations to be declared profile-similar, the calculated f_2 value must fall within the globally accepted regulatory range of 50 to 100. Values approaching 100 demonstrate absolute curve congruence, thereby establishing the in vitro performance equivalence and sameness of the test and reference products. The dissolution medium preparation and volume is mentioned in Table 2.

Table 2 Preparations of Dissolution Medium

Medium	Components	Preparation Methodology	Final Volume	Target pH
Acid Buffer (pH 1.2)	0.1N HCl	Dilute 102.0 mL of concentrated HCl (37%) with purified water.	12,000 mL	1.2 ± 0.05
Acetate Buffer (pH 4.5)	Sodium Acetate, Acetic Acid	Dissolve 35.88 g sodium acetate and 19.2 mL acetic acid in water, adjust pH.	12,000 mL	4.5 ± 0.05
Phosphate Buffer (pH 6.8)	KH_2PO_4, NaOH	Dissolve 81.6 g KH_2PO_4 and 10.9 g NaOH in water, adjust pH.	12,000 mL	6.8 ± 0.05

Note: Final volume and pH must be verified prior to testing.

2.5.2 Procedure

The dissolution testing was executed in a light-resistant environment. Individual dissolution vessels (n = 6) were filled with 900 mL of the designated medium and maintained at an equilibrated temperature of 37 ± 0.5 °C. One capsule was deployed into each vessel, and the testing sequence was initiated immediately for a 60-minute runtime.

2.5.3 Sample Preparation

At each designated sampling interval, an approximate 20 mL aliquot of the dissolution medium was withdrawn and clarified via filtration through Whatman filter paper. Subsequently, a 5 mL volume of the filtrate was quantitatively transferred into a 100 mL volumetric flask. The sample was sequentially treated with 50 mL of deionized water and 5 mL of 5 M sodium hydroxide. The mixture was then diluted to volume with deionized water and homogenized thoroughly. To ensure kinetic reproducibility, the absorbance of the final solution was measured precisely 6 minutes following the addition of the sodium hydroxide reagent.

2.5.4 Standard Preparation

An accurately weighed amount of Tetracycline Hydrochloride working standard (0.090 g) was transferred into a 100 mL volumetric flask. The standard matrix was solubilized by adding 70 mL of dissolution medium, aided by stirring and/or sonication until completely dissolved. The flask was filled to the 100 mL mark with the identical medium, mixed well, and passed through a Whatman filter paper. To prepare the working concentration for absorbance measurement, a 2 mL portion of the filtered standard solution was transferred into another 100 mL volumetric flask. Deionized water (50 mL) and 5 M sodium hydroxide (5 mL) were added sequentially. The solution was diluted to volume with deionized water, mixed thoroughly, and the absorbance was measured exactly 6 minutes after the introduction of the sodium hydroxide matrix.

2.5.5 Analysis

The percentage of Lymecycline released into the dissolution medium was calculated based on the recorded spectrophotometric absorbance relative to the declared content of the Tetracycline Hydrochloride reference standard. Stoichiometric conversion factors were applied to determine the equivalent active concentrations: each milligram of Tetracycline Hydrochloride was taken as equivalent to 0.9241 mg of Tetracycline base, and the derived Tetracycline value was subsequently scaled by a factor of 1.356 to quantify the corresponding concentration of Lymecycline.

2.5.6 Calculation

$$\%\text{age of Tetracycline} = \frac{\text{Absorbance of Sample}}{\text{Average Absorbance of Standard}} \times \frac{\text{Dil. of Standard} \times 0.9241}{\text{Dilution of Sample}} \times \text{Potency of W.S}$$

$$\%\text{age of Lymecycline} = \%\text{age of Tetracycline} \times 1.356 = \text{———}\%\text{(as labeled)}$$

(1) x Mean ($\bar{X}$) = $\sum$ x (Sum of all the readings) / N (total number of readings)

(2) % Co-efficient of Variation (CV or RSD) = Std. Dev. / Mean × 100

(3) Difference Factor (f1) = $\{[\sum^{n}_{t=1} (R_t - T_t)] / [\sum^{n}_{t=1} R_t]\} \times 100$

(4) Similarity Factor (f2) = $50 \times \text{LOG} \{[1+(1/n) \times \sum^{n}_{t=1} (R_t - T_t)^2]^{-0.5} \times 100\}$

2.5.7 Acceptance Criteria

(1) % Coefficient of Variation (CV) $< 20\%$ for time points up to 10 minutes and $< 10\%$ for other time points.

(2) Both Reference product & Test product shows more than 85% mean drug release within 15 minutes (no calculation required)

(3) Difference Factor (f1) value $\leq$ 15

(4) Similarity Factor (f2) value $\geq$ 50 (50 – 100)

Reference product and in-House product details for in vitro study is described in Table 3.

Table 3 Product Description for *in vitro* study

Description	Reference / Comparator Product	Test Product
Product Name	Tetralysal® 300 mg Capsule	Lyme 300 mg Capsule
Dosage Form	Hard Gelatin Capsule	Hard Gelatin Capsule
Composition	Lymecycline 408 mg (equiv. to 300 mg Tetracycline)	Lymecycline (BP) 408 mg (equiv. to 300 mg Tetracycline)
Lot / Batch #	4010	T-001
Mfg. / Exp. Date	07-2023 / 07-2026	02-2024 / 01-2026
Manufacturer	Sophartex (France)	Skims Pharmaceuticals (Pakistan)

The innovator (reference) product employed for comparative in vitro evaluation is presented in Figure 7.

Figure 7 Reference Product used for in-Vitro Study

2.6 Excipient compatibility study

2.6.1 A Description of the Drug-Excipient Samples

In Table 4, API and others in-active material were prepared & tested for compatibility Study also mentioned the role of each ingredient.

Table 4 Description of Lymecycline formulation under the compatibility study

Sr.	Sample (Lymecycline) Preparation		
	Ingredient	Quantity(mg) / Capsule	Role Ingredient
1	Lymecycline	408	API
2	Magnesium Stearate	6.483	Glidant
3	Aerosil-200	3.00	Lubricant
4	Hard Gelatin capsule Shell	100	To enclosed medicine

2.6.2 Drug Substance-Excipient Compatibility Study

To evaluate drug–excipient compatibility, the active pharmaceutical ingredient (API) alone and its respective binary mixtures with magnesium stearate, Aerosil-200, and empty capsule shell material were prepared in the solid state according to the ratios defined in Table 1. These samples were subsequently stored under accelerated stress conditions (40 °C ± 2 °C / 75% ± 5% RH) for a duration of one month. Chemical compatibility was assessed quantitatively via high-performance liquid chromatography (HPLC) and expressed as percent assay recovery relative to the reference standard, with the compiled data summarized in the Excipient Compatibility Study Report (Table 11). Furthermore, comprehensive long-term stability profiling of the finished capsules packaged in Alu–Alu blister packs was executed under both accelerated (40 °C ±

2 °C / 75% ± 5% RH) and real-time/room-temperature (25 °C ± 2 °C / 60% ± 5% RH) environments for up to six months. Critical quality attributes (CQAs)—including physical appearance, uniformity of dosage units, moisture content, identification, dissolution profile, and chemical assay—were monitored sequentially and are summarized in Table 12.

3 Results and Discussion

3.1 Formulation Development

3.1.1 Active Ingredient

Lymecycline B.P 408 mg (equivalent to 300 mg Tetracycline base).

3.1.2 Excipients Selection

All excipients utilized in the final capsule formulation were selected based on robust solid-state compatibility studies. The selected components are pharmacopeial-grade and possess a well-documented history of safe use in various commercial oral dosage forms. The representative chromatograms illustrating the baseline resolution of the Tetracycline Hydrochloride reference standard, the Lymecycline formulation sample, and the blank matrix preparation are displayed in Figures 8, 9, and 10, respectively.

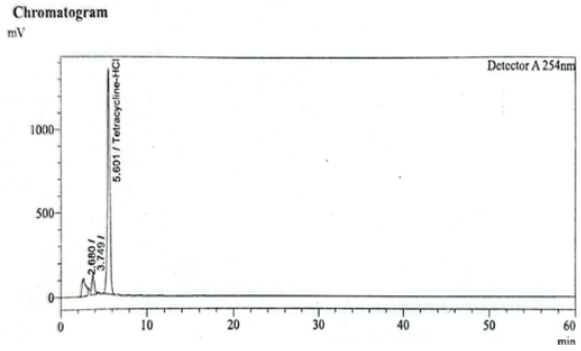

Figure 8 HPLC Report/ Chromatogram for Tetracycline HCl Reference

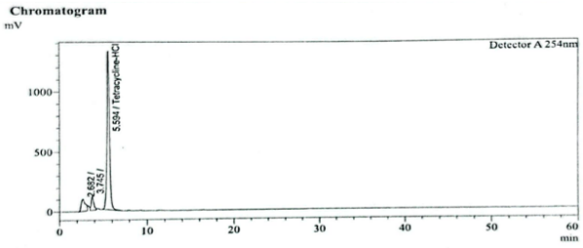

Figure 9 HPLC Report/ Chromatogram for Lymecycline (Lyme 300mg) Test Sample

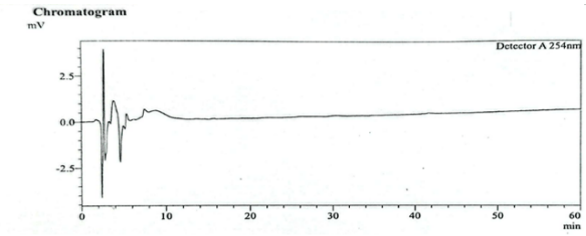

Figure 10 HPLC Report/ Chromatogram Blank Solution (Diluent)

Figures 8, 9, and 10 illustrate key aspects of the development of Lyme 300 mg Capsules, which contain Lymecycline BP 408 mg (equivalent to 300 mg of Tetracycline base). The formulation was designed with a focus on achieving consistent drug performance, stability, and patient compliance. A well-structured formulation approach ensured optimal selection of excipients, hard capsule fill properties, and manufacturing parameters. This strategic development process

aimed to produce a robust and reproducible dosage form that meets regulatory and quality standards.

The figures support the formulation design by showing data from validated analytical methods used to ensure the quality and uniformity of the final product. This ensures that every batch of Lyme 300 mg Capsules consistently meets the required specifications throughout its shelf life. Together, the formulation strategy and analytical validation demonstrate a scientifically sound development process, contributing to the product's overall safety, efficacy, and quality. These figures collectively highlight the technical and regulatory diligence involved in bringing Lyme 300 mg Capsules to a stable and market-ready pharmaceutical product.

3.2 Comparative Dissolution Profile Results:

The obtained value in acidic medium of reference product is provided in Table 5 and Graphically presentation for reference and test product (pH 1.2) is given Figure 11 for CDP.

Table 5 Comparative Dissolution Profile in Acidic Medium (pH 1.2) for Reference Product

Time Point (min)	Mean Release (%) ± SD	% RSD	Observation Notes
10	–	–	Not Collected*
15	–	–	Not Collected*
30	–	–	Not Collected*
45	44.40 ± 0.81	1.82	Recorded
60	96.89 ± 0.96	0.99	Recorded
75	97.18 ± 0.88	0.91	Recorded

Note: * Early dissolution time points (10, 15, 30 min) were not collected.

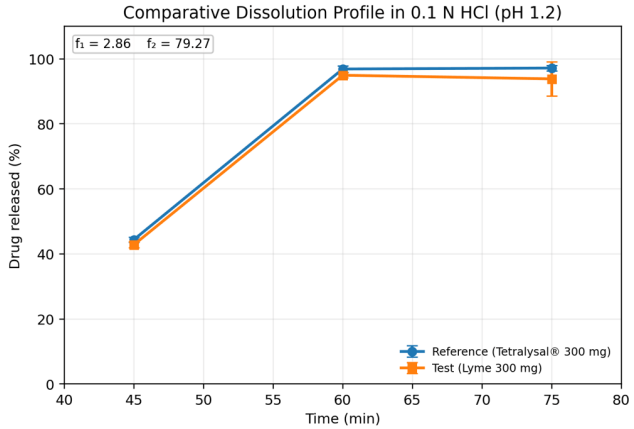

Figure 11 Graphical presentation of CDP for reference and test product (pH 1.2)

The obtained value in acidic medium of product is shown in Tables 6 and 7.

Table 6 Comparative Dissolution Profile in Acidic Medium (pH 1.2) for Test Product

Time Point (min)	Mean Release (%) ± SD	% RSD	Observation Notes
10	–	–	Not Collected*
15	–	–	Not Collected*
30	–	–	Not Collected*
45	42.83 ± 0.90	2.11	Recorded
60	94.97 ± 0.82	0.86	Recorded
75	93.85 ± 5.27	5.61	Recorded

Note: * Early dissolution time points (10, 15, 30 min) were not collected.

Table 7 Mathematical Comparison (pH 1.2: Test *vs.* Reference)

Parameter	Calculated Value	Acceptance Criteria	Conclusion
Difference Factor (f_1)	2.86	$\leq$ 15	Complies
Similarity Factor (f_2)	79.27	50–100	Similar

The obtained dissolution values of the reference product in acetate buffer (pH 4.5) are presented in Table 8, while the graphical comparison of the reference and test products at pH 4.5 is shown in Figure 12 for CDP evaluation.

Table 8 Comparative Dissolution Profile in Acetate Buffer (pH 4.5) for Reference Product

Time Point (min)	Mean Release (%) ± SD	% RSD	Observation Notes
10	–	–	Not Collected*
15	–	–	Not Collected*
30	–	–	Not Collected*
45	47.39 ± 1.76	3.71	Recorded
60	55.39 ± 1.13	2.03	Recorded
75	61.37 ± 0.86	1.41	Recorded

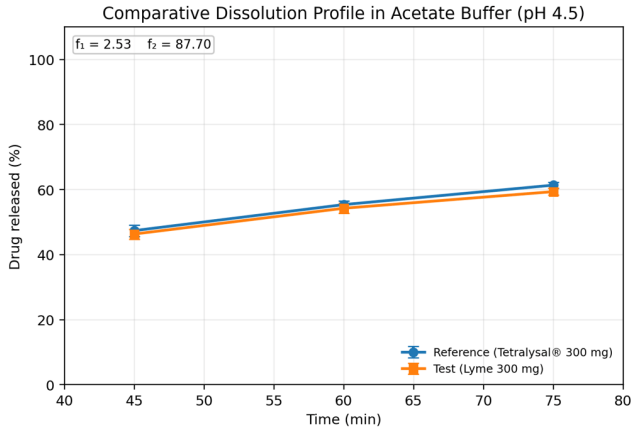

Figure 12 Graphically presentation of CDP for reference and test product (pH 4.5)

The obtained values in Acetate Buffer (pH 4.5) of product is given in Tables 9 and 10.

Table 9 Comparative Dissolution Profile in Acetate Buffer (pH 4.5) for Test Product

Time Point (min)	Mean Release (%) ± SD	% RSD	Observation Notes
10	–	–	Not Collected*
15	–	–	Not Collected*
30	–	–	Not Collected*
45	46.34 ± 1.53	3.31	Recorded
60	54.27 ± 1.53	2.82	Recorded
75	59.38 ± 1.00	1.68	Recorded

Table 10 Mathematical Comparison (pH 4.5: Test *vs.* Reference)

Parameter	Calculated Value	Acceptance Criteria	Conclusion
Difference Factor (f_1)	2.53	$\leq$ 15	Complies
Similarity Factor (f_2)	87.70	50 – 100	Similar

The obtained value in Phosphate Buffer (pH 6.8) of reference product is given in Table 11 and comparative graphical representation for reference and test product for pH 6.8 is provided in Figure 13.

Table 11 Comparative Dissolution Profile in Phosphate Buffer (pH 6.8) for Reference Product

Time Point (min)	Mean Release (%) ± SD	% RSD	Observation Notes
10	–	–	Not Collected*
15	–	–	Not Collected*
30	–	–	Not Collected*
45	33.22 ± 1.24	3.74	Recorded
60	38.43 ± 0.75	1.95	Recorded
75	40.14 ± 1.07	2.65	Recorded

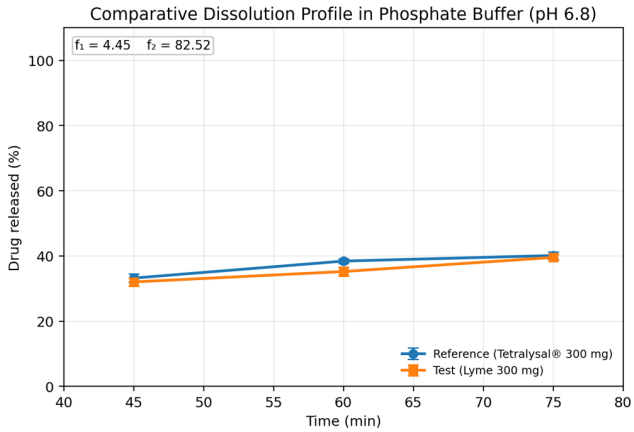

Figure 13 Graphically presentation of CDP for reference and test product (pH 6.8)

The obtained value in Phosphate Buffer (pH 6.8) of product is given in Tables 12 and 13.

Table 12 Comparative Dissolution Profile in Phosphate Buffer (pH 6.8) for Test Product

Time Point (min)	Mean Release (%) ± SD	% RSD	Observation Notes
10	–	–	Not Collected*
15	–	–	Not Collected*
30	–	–	Not Collected*
45	32.03 ± 1.22	3.81	Recorded
60	35.23 ± 1.39	3.94	Recorded
75	39.55 ± 0.84	2.11	Recorded

Table 13 Mathematical Comparison (pH 6.8: Test *vs*. Reference)

Parameter	Calculated Value	Acceptance Criteria	Conclusion
Difference Factor (f_1)	4.45	$\leq$ 15	Complies
Similarity Factor (f_2)	82.52	50–100	Similar

A comparative dissolution study was conducted between the test product, Lyme 300 mg Capsules, and the reference product, Tetralysal 300 mg Capsules. The difference factor (f_1) was calculated in Acidic medium pH 1.2 in Tables 5 and 6 is 2.86%, and the similarity factor (f_2) was 79.27%, in acetate buffer pH 4.5 is calculated in Tables 7 and 8 (f_1) is 2.53% and (f_2) is 87.70% and in phosphate buffer pH 6.8 is calculated in Tables 9 and 10 (f_1) is 4.45% and (f_2) is 82.52%. These values fall within the acceptable regulatory limits (f1 $<$ 15 and f2 $>$ 50), indicating a high degree of similarity between the dissolution profiles of the two products. Both the test and reference formulations exhibited more than 75% drug release within 75 minutes in an acidic medium, which is a key requirement for immediate-release formulations. Additionally, the dissolution behavior was found to be comparable in acetate buffer (pH 4.5) and phosphate buffer (pH 6.8), further supporting the consistency of drug release across different physiological pH conditions. These findings confirm that the test product meets the regulatory criteria for dissolution profile similarity, providing strong evidence of in vitro study. As such, the data support the conclusion that Lyme 300 mg Capsules perform similarly to Tetralysal 300 mg Capsules, and can be considered pharmaceutically equivalent in terms of dissolution behavior.

3.3 Analytical Method Verification

The analytical method for Lyme 300 mg Capsules was verified in accordance with ICH Guideline Q2 (R1), November 2005, confirming its suitability for routine quality control. System suitability parameters including %RSD (0.19%), tailing factor (1.63), and theoretical plates (5620) met all acceptance criteria, demonstrating system precision and chromatographic efficiency. The method showed excellent specificity, with no interference observed from placebo or blank preparations at the retention time of the active ingredient in both standard and sample solutions. Accuracy was confirmed through recovery studies, with results ranging from 99.70% to 101.25%, well within acceptable limits. Robustness testing showed that the method remained stable over 4 hours, even under slight pH variations, with consistent chromatographic results.

The method also demonstrated high precision, with repeatability and intermediate precision values of 0.25% and 0.44% RSD, respectively. Additionally, the method satisfied criteria for linearity and range, further supporting its reliability. Overall, the method was proven to be accurate, precise, specific, robust, and suitable for its intended analytical purpose. The compatibility study results are calculated and %age of recovery with each in-active material is described in Table 14.

Table 14 Excipient Compatibility Study Results of Lymecycline 408 mg Formulation

Sr.	Solid-State Composition	Theoretical Contents	Weight (mg, Std / Spl)	Concentration (mg/mL)	HPLC Peak Area (mAU)	% Assay (Recovery)	Acceptance Range	Conclusion
1	Standard (API Alone)	100.0%	Std: 325.000 Spl: 408.000	Std: 0.1625 Spl: 0.2040	Std: 2182577.6 Spl: 2187253.0	100.03%	95.0% – 105.0%	Compatible
2	API + Magnesium Stearate	100.0%	Std: 325.000 Spl: 414.483	Std: 0.1625 Spl: 0.2040	Std: 2182577.6 Spl: 2158951.0	98.74%	95.0% – 105.0%	Compatible
3	API + Aerosil-200	100.0%	Std: 325.000 Spl: 411.000	Std: 0.1625 Spl: 0.2040	Std: 2182577.6 Spl: 2150625.0	98.36%	95.0% – 105.0%	Compatible
4	API + Empty Capsule Shell	100.0%	Std: 325.000 Spl: 508.000	Std: 0.1625 Spl: 0.2040	Std: 2182577.6 Spl: 2165903.0	99.05%	95.0% – 105.0%	Compatible

Note: Analyzed after 1-Month Storage under Accelerated Stress Conditions (40 °C ± 2 °C / 75% RH ± 5%)

3.3.1 Table Technical Notes & Regulatory Observations

(1) Sample Weight Calculations: The sample weight (Spl) accurately accounts for the active 408 mg of Lymecycline blended with the exact proportional weight of the respective functional excipient required for a single capsule unit (6.483 mg Magnesium Stearate, 3.000 mg Aerosil-200, and 100.000 mg Capsule Shell).

(2) Chromatographic Parameters & System Suitability: 'Std' refers to the Reference Standard solution; 'Spl' refers to the respective stability storage blend sample. The exceptional reproducibility of the standard HPLC peak area (2182577.6) demonstrates system suitability and chromatographic integrity throughout the sequence.

(3) Final Analytical Evaluation Summary: The chosen excipients in this solid oral generic formulation (Lymecycline 408 mg, equivalent to 300 mg Tetracycline Base) exhibit complete chemical compatibility. No significant quantitative degradation, recovery drops below threshold limits, or novel impurity peaks were observed under accelerated climate conditions over 1 month, validating blend stability.

3.4 Stability Study (Accelerated Conditions):

A formulation stability study of Lyme 300 mg Capsules (Filled in ALU-ALU Foil having 7 hard capsule/ Blister) conducted under accelerated conditions (40°C ± 2°C / 75% RH ± 5%) up to six month yielded satisfactory results, indicating physical and chemical studies.

The chosen excipients in the formulation (Lymecycline 408 mg, equivalent to 300 mg Tetracycline Base) were found to be compatible, with no adverse interactions observed under one month of accelerated conditions (40°C ± 2°C / 75% RH ± 5%).

4 Discussion

The development of Lyme 300 mg Capsules, containing Lymecycline BP 408 mg (equivalent to 300 mg Tetracycline base), demonstrated robust formulation design supported by comprehensive analytical and stability data. All selected excipients were pharmacopeial and proven compatible through pre-formulation and accelerated compatibility studies, ensuring stability and safety of the product. Comparative dissolution testing revealed high similarity to the reference product, Tetralysal 300 mg, with an f1 value of 2.87% and f2 value of 79.27%, confirming dissolution equivalence across various media and supporting in vitro study. Analytical method verification, performed in accordance with ICH Q2(R1), confirmed system suitability, specificity, accuracy (recovery 99.70%–101.25%), precision (repeatability and intermediate % RSD $<$ 0.5%), robustness, and linearity ensuring the method's reliability for routine quality control. Stability studies under ICH-recommended accelerated conditions (40°C ± 2°C / 75% RH ± 5%) over six months demonstrated that the formulation remained physically and chemically stable, with no significant changes or interactions observed, especially when packaged in ALU-ALU blister packs. Collectively, these results validate the formulation's quality, safety, and regulatory compliance, positioning it for successful market approval [21–24]. Table 15 shows Comprehensive Stability Summary Report Lymecycline 408 Mg Hard Capsule and Figure 14 shows summarization of formulation selection, analytical verification, and comparative dissolution

assessment of the generic lymecycline capsule.

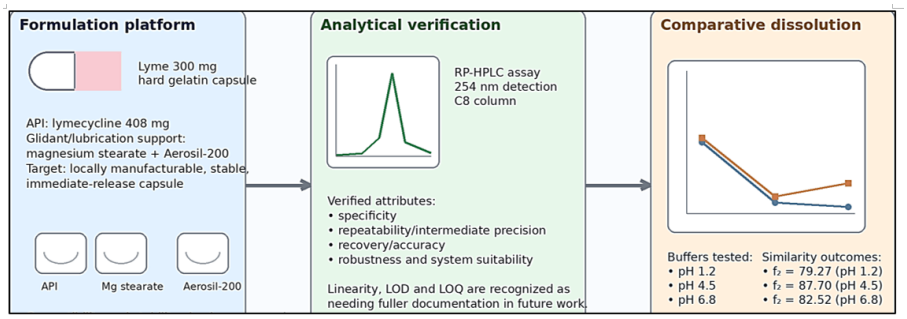

Figure 14 Summarization of formulation selection, analytical verification, and comparative dissolution assessment of the generic lymecycline capsule.

Table 15 Comprehensive Stability Summary Report (Lymecycline 408 mg Hard Capsules)

Parameter	Specification Limits	Acc 1M	Acc 3M	Acc 6M	RT 1M	RT 3M	RT 6M
Physical Characteristics	Pink/White size '0' capsule; yellow powder	Complies	Complies	Complies	Complies	Complies	Complies
Uniformity of Weight	600 mg ± 10% (540 – 660 mg)	600.3 mg	599.0 mg	598.8 mg	601.1 mg	604.1 mg	596.3 mg
Water Content (%)	NMT 7.0%	4.50%	4.58%	4.72%	4.52%	4.47%	4.91%
Identification	Must correlate positively	Complies	Complies	Complies	Complies	Complies	Complies
Dissolution (%)	NLT 80% (Q) in 60 minutes	95.10%	93.12%	92.41%	95.01%	93.81%	92.44%
Assay (%)	90.0% – 110.0%	100.38%	99.90%	99.82%	100.18%	99.98%	100.04%

Note: Storage Conditions: Accelerated (Acc) = 40 °C/75% RH; Real-Time (RT) = 25 °C/60% RH; 408 mg Lymecycline corresponds to 300 mg Tetracycline base; The product was found stable up to 6 months under accelerated and real-time storage conditions as per ICH Q1A (R2) guidelines for climatic Zone IVa.

5 Limitations and Future Work

The dissolution dataset begins at 45 min, which is later than preferred for immediate-release similarity assessment. Additional sampling at 10, 15, 20, and 30 min would allow clearer evaluation of rapid-release behavior and would strengthen f2-based comparisons.

The assay procedure performed well for the documented verification attributes, but a complete validation package under current expectations should include explicit calibration-line statistics, range justification, LOD, LOQ, and ideally forced-degradation evidence demonstrating stability-indicating behavior.

The development strategy was risk-informed but not a full QbD program. Future work should therefore include structured design-of-experiments, identification of critical material attributes and process parameters with quantitative response modeling, and prospective establishment of a justified operating space.

Finally, this study supports in vitro pharmaceutical equivalence only. Therapeutic interchangeability and definitive bioequivalence would require either an acceptable biowaiver route supported by the relevant regulatory framework or direct in vivo evidence, depending on the product classification and jurisdiction

6 Conclusion

The Lyme 300 mg Capsule demonstrates in vitro pharmaceutical equivalence with the reference product (Tetralysal 300 mg) in accordance with WHO Annex 3, Section 2.2.4, covering equivalence and dissolution studies. This is supported by f_1/f_2 values and comparable dissolution profiles across multiple pH conditions. The developed generic lymecycline hard gelatin capsule demonstrated acceptable analytical performance, short-term excipient compatibility, supportive stability results, and comparative dissolution similarity with the reference product across pH 1.2, 4.5, and 6.8 media. The formulation is physically and chemically stable, with all excipients confirmed to be compatible under accelerated stability testing. The analytical methods used for assay and quality control are fully validated and verified, meeting all predefined acceptance criteria for specificity, accuracy, precision, robustness, linearity, range, and system suitability. Therefore, the product is considered pharmaceutically equivalent and analytically reliable. Additionally, six months of stability studies conducted according to ICH Q1A(R2) confirm that the product meets all required chemical and physical specifications.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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