



To Compare And In-Vitro Evaluation Of Dissolution Profiles Of Clarithromycin By Biowaiver Study

Kolapkar Mrunal, Dr. Tambe Sagar

Samarth institute of Pharmacy, Belhe

Abstract:

Clarithromycin is an antibiotic widely used for the treatment of various bacterial infections, including respiratory tract infections, skin infections, and *Helicobacter pylori* eradication. This comparative study aims to evaluate the efficacy, safety, and pharmacokinetic properties of generic clarithromycin versus the brand-name version. The study involved a randomized, controlled trial with two groups of patients, one receiving generic clarithromycin and the other receiving the branded formulation. Primary endpoints included clinical effectiveness, microbiological eradication rates, and adverse events. Secondary endpoints assessed pharmacokinetics, such as bioavailability and half-life. Results indicated that both the generic and brand-name formulations were equally effective in treating infections, with no significant difference in the rate of adverse effects. Pharmacokinetic analysis showed comparable absorption and elimination profiles for both formulations. These findings suggest that generic clarithromycin is a viable and cost-effective alternative to the standard brand-name version, offering similar clinical outcomes and safety profiles. potential for substitution with the standard drug under appropriate circumstances.

Keywords: Clarithromycin, Biowaiver, Dissolution Profiles, Regulatory guidelines, in vitro testing, IVIVC, Dissolution methods.

Introduction:

Clarithromycin is a widely used macrolide antibiotic prescribed for bacterial infections, including respiratory tract infections, skin infections, and *Helicobacter pylori* eradication in peptic ulcer disease. Available in both branded (standard) and generic formulations, it is crucial to evaluate their comparative efficacy, safety, and bioequivalence to ensure optimal patient outcomes.

Generic medications are designed to be therapeutically equivalent to their branded counterparts, meeting regulatory standards for bioavailability and pharmacokinetics. However, differences in excipients, manufacturing processes, and dissolution rates can sometimes lead to variations in drug absorption and clinical effectiveness. This study aims to compare the efficacy, pharmacokinetics, and safety of generic clarithromycin with its branded counterpart to determine their interchangeability in clinical practice.[1]

Clarithromycin is an acid-stable orally administered macrolide antimicrobial drug, structurally related to erythromycin. It has a broad spectrum of antimicrobial activity, similar to that of erythromycin and inhibits a range of Gram-positive and Gram-negative organisms, atypical pathogens and some anaerobes. Significantly, clarithromycin demonstrates greater in vitro activity than erythromycin against certain pathogens including *Bacteroides melaninogenicus*, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, *Mycobacterium chelonae* subspecies--*chelonae* and--*abscessus*, *Mycobacterium leprae*, *Mycobacterium marinum*, *Mycobacterium avium* complex, *Legionella* spp. and, when combined with its 14-hydroxy metabolite, against *Haemophilus influenzae*. However, bacterial strains resistant to erythromycin are also generally resistant to clarithromycin. The antimicrobial activity of clarithromycin appears to be enhanced by the formation in vivo of the microbiologically active 14-hydroxy metabolite. The clinical efficacy of clarithromycin has been confirmed in the treatment of infections of the lower and upper respiratory tracts (including those associated with atypical pathogens), skin/soft tissues, and in paediatrics. Clarithromycin was as effective as erythromycin and other appropriate drugs including beta- lactams (penicillins and cephalosporins) in some of the above infections. A most promising indication for clarithromycin appears to be in the treatment of immunocompromised patients infected with *M. avium* complex, *M. chelonae* sp. and *Toxoplasma* sp. Small initial trials in this setting reveal clarithromycin alone or in combination with other antimicrobials to be effective in the eradication or amelioration of these infections. Noncomparative studies have provided preliminary evidence for the effectiveness of clarithromycin in the treatment of infections of the urogenital tract, oromaxillo facial and ophthalmic areas. [23]

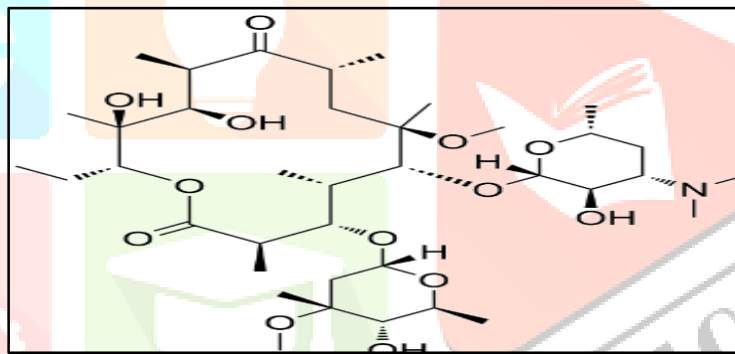


Fig.1. Chemical structure of Clarithromycin

IUPAC name: (3R)-1-Azabicyclo [2 2 2] oct-3-yl (1S)-1-phenyl-3, 4 Dihydroisoquinoline-2 (1H)-carboxylate

Molecular formula: C₂₃H₂₆N₂O₂C₄H₆O₄

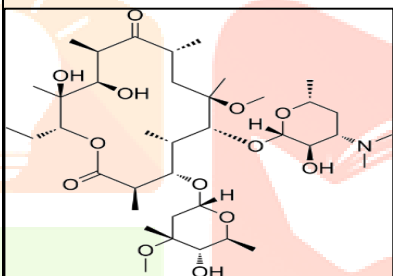
Molar mass: 362.473 g/mol–1

Clarithromycin is a medication used primarily for the treatment of overactive bladder (OAB), a condition characterized by symptoms such as urgency, frequency, and urge incontinence. It belongs to a class of drugs known as antimuscarinics or anticholinergics. Clarithromycin works by blocking certain receptors in the bladder, reducing involuntary contractions and improving bladder control. Clarithromycin is well absorbed after oral administration, reaching peak concentrations in the blood within 3-8 hours. It extensively binds to plasma proteins and distributes into tissues, particularly in the liver and kidneys. Primarily metabolized by the liver through the cytochrome P450 system, particularly the CYP3A4 enzyme. Elimination occurs mainly through the kidneys, with approximately 69% of the administered dose excreted in the urine. ⁽⁴⁾[12]

Dissolution testing:

Dissolution testing is a surrogate for in vivo performance that shows the rate and extent a drug is released. UV spectrophotometry is an appropriate method for dissolution profiling, which allows for the monitoring of drug concentration at various times in the dissolution medium. The reason for selecting this methodology is due to its sensitivity and specificity in the quantification of Clarithromycin. Comparative dissolution profiling is a technique of determining how generic drugs and standard drugs dissolve over time. Dissolution test of Clarithromycin tab was conducted over time to compare the rates of releasing these batches of formulations. The parameters to consider in the comparative dissolution profiling are the dissolution media, paddle speed, and the sampling time. The reason for considering consistency in the methodologies is to present credible results and for the acquisition of regulatory approval, hence achieving bioequivalence of generic and standard Clarithromycin tab.[17]

Drug Profile:

Parameter	Information
Drug Name	Clarithromycin
Brand Name	Aliclair
Structure	
Weight	747.95 g/mol
Chemical formula	C ₃₈ H ₆₉ FNO ₁₃
IUPAC Name	(6R,7R,9R,10R,11R,12R,13S,14R)-6-[(2S,3R,4S,6R)-4-Dimethylamino-3-hydroxy-6-methyloxan-2-yl]oxy-14-ethyl-12,13-dihydroxy-10,11-dimethoxy-3,7,9,11,13-pentamethyl-1-oxa-cyclotetradecan-2-one
BCS Class	Class II
Half life	3–7 hours (depends on dose and metabolism)
Pka	8.99
Log P	3.16
Particle size	Depends on formulation, but micronized or nano sized particles are often used to improve bioavailability.
Hygroscopicity	Slightly hygroscopic
Polymorphic form	Clarithromycin does not typically exist in a polymeric form but can be formulated with polymers to enhance stability and solubility

Solid state Stability	Sensitive to moisture and acidic conditions; degradation can occur via hydrolysis
Melting Point	217–220°C
T max	2– 4 hours after oral administration
Solubility	water solubility, soluble in organic solvents like methanol, ethanol

Material:

DESCRIPTION	BRANDED	GENERIC
Colour	Yellow	Off- white
Shape	Oval	Round
Smell	Slightly fruity odor	Slightly fruity odor
Coat	Film coated	Film Coated
Contain	romycin (Macrolide Antibiotic)	romycin (Macrolide Antibiotic)
Brand name	Aliclair 250 mg	Zoclar 250 mg
Manufactured By	ord Healthcare ltd.	Mfg. Cipla Ltd. India

Table 1: Details of Drug

Sr. No.	Instrument	Make	Software	Model No.
1.	solution Test Apparatus	LABINDIA	NA	DS 8000
2.	UV – Spectrophotometer	LABMAN	space pro	SP- UV 100B
3.	Analytical Balance	WENSAR	NA	DS 8000
4.	pH Meter	LABMAN	NA	LMPH-10
5.	Ultra Sonicator	LABMAN	NA	LMUC3
6.	Disintegration Tester (USP)	ELECTROLAB	NA	ED -2 SAPO

Table 2. Instruments

Methodology:**Evaluation Test for Tablets:****1. Diameter and Thickness –**

Vernier caliper measure the tablet's diameter and thickness at multiple points to ensure uniformity. Confirming consistent size for accurate dosing and ease of swallowing. Take 10 tablets of branded and generic Clarithromycin tab and determine the diameter and thickness of each individual tablet.

Calculate the average value. (Table 6 and 7).[19]

2. Uniformity of weight test:

Take 20 tablets of generic and branded Clarithromycin tab respectively (Table - 5). Weigh individual tablet. Determine the weight of each tablet using following formula –

$$(-) \text{ Deviation} = (\text{lowest weight} - \text{Average weight} / \text{Average weight}) \times 100$$

$$(+) \text{ Deviation} = (\text{Highest weight} - \text{Average weight} / \text{Average weight}) \times 100$$

3. Average weight:

Weigh together 10 tablets of generic and calculate the average weight. Weigh together 10 tablets of branded Clarithromycin and calculate the average weight. (Table-4)

Average weight (mg) = $W/10$ Where, W = Weight of 10 tablets in mg.

4. Hardness Test:

Tablet hardness is an important parameter for giving optimum effect in body. If the tablet is too hard it will not disintegrate at required time and fail to meet the dissolution specification, if it is too soft that will create difficulties in transporting the tablets. Monsanto Hardness Tester is used. The force applied to the edge of the tablet was gradually increased by moving the screw knob forward until the tablet was broken. Ten tablets were randomly selected from each brand and the pressure at which each tablet crushed was recorded.[29]

5. Disintegration Test:

The disintegration time of a tablet refers to how quickly it breaks down into smaller particles when exposed to a liquid environment, typically in the gastrointestinal tract. This parameter is important for assessing the tablet's ability to release the active ingredient for absorption.[25] Six tablets from branded and generic Clarithromycin were employed for the test in distilled water at 37 ± 0.5 °C using a Tablet Disintegration Tester, the disintegration time (DT) was taken as the time when no particle remained on the basket of the system. ⁽¹⁰⁾

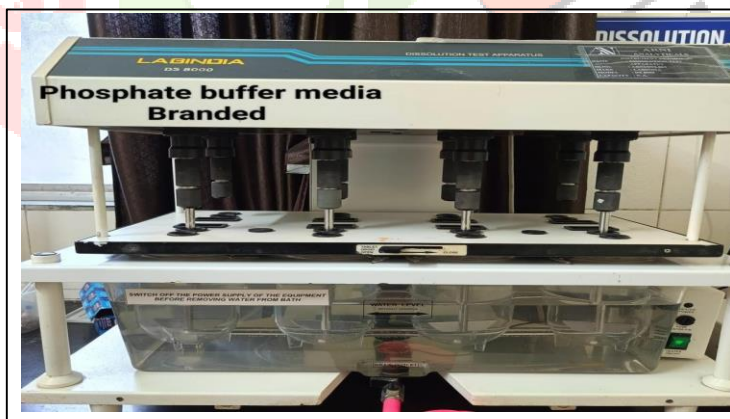


Fig. No. 3 - Disintegration test of Clarithromycin -10 tablet

In Vitro Dissolution Test:

The drug release rate of branded and generic Clarithromycin tablets were determined by using United States Pharmacopeia (USP) dissolution testing apparatus type 2 (paddle). The dissolution test was performed by using 900 ml of dissolution medium at $37^{\circ}\pm 0.50^{\circ}$ C and 50 rpm. In specified time intervals an aliquot of 5ml samples of the solution were withdrawn from the dissolution apparatus and with replacement of fresh fluid to dissolution medium. The samples were filtered through filter paper of $0.45\ \mu\text{m}$. Absorbance of these solutions were measure at λ - max 220 nm of Clarithromycin by using UV-Visible Spectrophotometer. The drug release of tablet was plotted against time to determine the release of selected generic and branded drugs.[11]

Fig. No. 4 –Dissolution Test Clarithromycin -10 in Phosphate



buffer (pH 6.8) media

Method of analysis:

5.1 Dissolution conditions

Apparatus	: USP Type-II
Rotary speed of bowl	: 50 RPM
Dissolution medium	: Phosphate Buffer pH-6.8 Medium volume : 900 ml
Temperature of dissolution medium minutes	: $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ Test time : 45
Time Points	: 10, 20, 30, 45, 60 minutes.
UV Spectrophotometer Conditions:	
Wavelength:-	: 220nm

STANDARD SOLUTION:

Weigh accurately about 11mg of Clarithromycin working standard in 100ml volumetric flask, add 60ml of dissolution medium, sonicate for 5minutes to dissolve and makeup the volume with dissolution medium. Further dilute 5ml of the above solution to 50ml with dissolution medium.



Fig. No. 5- Preparation of Standard Solution

Dissolution conditions in 0.1M Hydrochloric Acid:

Apparatus	: USP Type-II
Rotary speed of bowl	: 50 RPM
Dissolution medium	: 0.1M Hydrochloric Acid
Medium's volume	: 900 ml
Temperature of dissolution medium	: 37 ° C ± 0.5 ° C
minutes.	Test time : 45
Time Points	: 10, 20, 30, 45, 60 minutes.

Calculation for f2:**LIMIT: 50 TO 100**

$$f_1 = \{[\sum_{t=1}^n |R_t - T_t|] / [\sum_{t=1}^n R_t]\} \cdot 100$$

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

Where,

R is the Reference (Innovator) Sample Result.

T is Test Sample Result t is time point

n is number of time points.

Plot graph of % Dissolution at each time point against time in minutes. For Both Reference and Test Batch

RESULTS AND DISCUSSION**1) DESCRIPTION OF GENERIC AND BRANDED****CLARITHROMYCIN TABLET 250 mg**

DESCRIPTION	Branded	GENERIC
Colour	Yellow	Off White
Shape	Oval	Round
Smell	Slightly fruity odor	Slightly fruity odor
Coat	Film coated	Film Coated
Contain	Clarithromycin Tablet 250 mg	Clarithromycin Tablet 250 mg
Brand name	Aliclair 250 mg	Zoclar 250 mg
Manufactured By	Mfg. By Lee ford Healthcare ltd.	Mfg. By Cipla Ltd. India

Table 3 – Description of branded and generic Clarithromycin Tablet

BRANDED TABLETS:-

Average weight (mg) = $W/10 = 2029/10$

Average weight of Branded tablets = 590.0

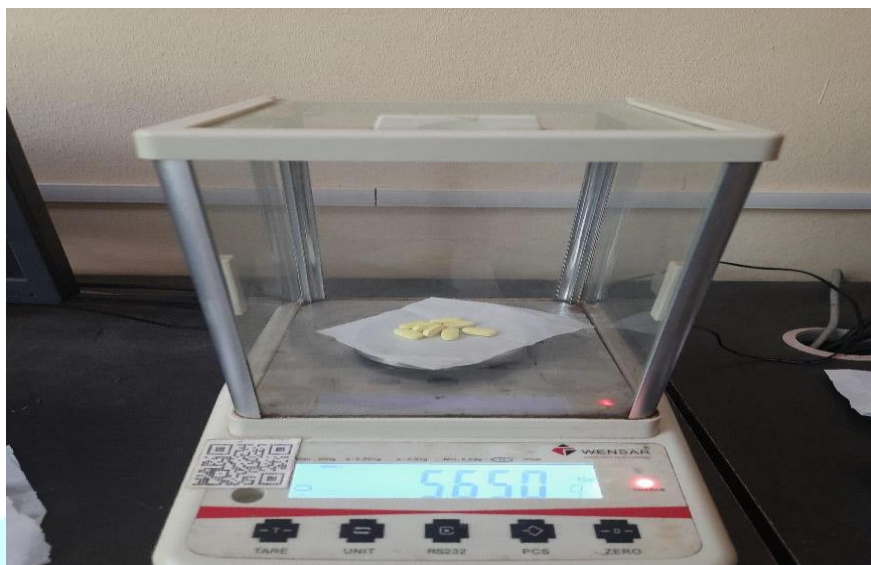


Fig. No. 6- Average Weight of Aliclair 250 mg

2) AVERAGE WEIGHT-

Weight together 10 Tablets selected at random and calculate the average weight.

Tab. No.	Branded (mg)	Generic (mg)
Average weight	590.0 mg	205.9 mg

Table 4: Average weight of branded and generic Clarithromycin Tablet

GENERIC TABLETS:

Clarithromycin Tablet

Average Weight (mg) = $W/10 = 2053/10$

Average weight of generic tablets = 440



Fig. No. 7- Average Weight of Zoclar 250 mg.

Conclusion:

Our research demonstrates that the in vitro dissolution profiles of generic and branded Clarithromycin tablets exhibit comparable characteristics under biowaiver conditions. Comparative Dissolution profiling of ZOCLAR-250 with ALICLAIR 250 was performed. Similarity (f_2) were calculated and found well within acceptance criteria. Hence the Phosphate Buffer pH-6.8 media is suitable for analysis. These findings suggest that, from a dissolution perspective, the generic formulation can be considered as a viable substitute for the branded counterpart. However, it is essential to emphasize the importance of additional bioequivalence studies and clinical trials to ensure equivalence in therapeutic efficacy and safety between the two formulations. Our study contributes valuable insights to the ongoing discourse on the interchangeability of generic and branded medications, paving the way for informed decision-making in pharmaceutical practice.

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