

# Paralleling the Quality and Economy of Levofloxacin Hemihydrate and Cefuroxime Axetil Tablets

Atmaram Pawar<sup>1,\*</sup>, Mahesh Chainpure<sup>2</sup>, Vividha Dhapte-Pawar<sup>1</sup>

<sup>1</sup>Department of Pharmaceutics, Poona College of Pharmacy, Bharati Vidyapeeth University, Erandwane, Pune, Maharashtra, INDIA.

<sup>2</sup>Department of Drug Regulatory Affairs, Poona College of Pharmacy, Bharati Vidyapeeth University, Erandwane, Pune, Maharashtra, INDIA.

## ABSTRACT

**Aim/Background:** The Government of India has initiated different regulations and provisions to provide low cost medicines at affordable rates than the high cost medicines. The government has initiated Jan Aushadhi stores in every city and village of India with the motto of promoting quality medicines for all at economic price. Improving the public perception and addressing their doubts regarding the quality and efficacy of low-cost medicines is a big challenge in this endeavour. **Materials and Methods:** In the present study, we have compared the low, medium and high cost medicines of biopharmaceutical classification system class I drug, levofloxacin hemihydrate and biopharmaceutical classification system class II drug, cefuroxime axetil, in order to verify their quality and efficacy. Existing low cost and medium cost brands of these drugs were selected and compared with their respective high cost products as per quality standards of Indian Pharmacopoeia viz. weight variation, friability, disintegration, assay and *in vitro* dissolution study specified in general and individual monographs. Moreover, *ex vivo* permeability and antimicrobial activities were assessed while comparing the efficacy of these products. **Results:** Findings from these studies revealed no significant differences between the efficacy of low cost, medium cost and high cost products. All products complied with the Indian Pharmacopoeia tests along with the comparable *ex vivo* permeation and antimicrobial activities for both the drugs. **Conclusion:** This study revealed that the low cost and medium cost tablets of levofloxacin hemihydrate and cefuroxime axetil can be used at par with the costlier tablets of same drugs.

**Key words:** Levofloxacin hemihydrate, Cefuroxime axetil, Generic, Microbial assay, Pharmacopoeial evaluation.

## INTRODUCTION

World Health Organization (WHO) and global drug regulatory agencies support the use of generic drugs (affordable alternative to innovator and branded medicines) to reduce the expenditure on high cost medicine significantly.<sup>1</sup> Especially in developing nations like India, government endorses the use of generic medicines to reach every needy person and improve the health of nation. Diverse regulatory agencies have different requirements for registration and promotion of generic drugs. Generic products have saved almost \$ 1.7 trillion USD in the US healthcare system (2002-2011). If two products are

pharmaceutically equivalent and their effect with respect to safety and efficacy are essentially same without direct proof, then it is therapeutically same as per WHO. Netherlands, Germany, Canada and UK have 20 %, 30 %, 50-30 %, 80 % higher price of branded drugs than generics, respectively. Promotion of economic drug products largely depends on government policies and programs.<sup>2</sup>

India, in context of generic pharmaceutical product manufacturing, by volume stands at third rank. Till 2020, the Indian pharmaceutical market is expected to grow \$72 billion USD sale from \$11 billion USD.

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**Correspondence:**

**Dr. Atmaram Pawar**

Professor of Pharmaceutics,  
Bharati Vidyapeeth University,  
Poona College of Pharmacy,  
Pune-411038, Maharashtra,  
INDIA.

Phone: +91 020-25437237

Email id: p\_atmaram@  
rediffmail.com



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In terms of exports, India stands at 17<sup>th</sup> rank. India exports generic products to more than 200 countries across the globe which include highly regulated markets of USA, Europe, Japan and Australia.<sup>3</sup> Central Drug Standard Control Organization (CDSCO), the drug regulatory authority of India, monitors the filing and approval process for drug and drug products. Drugs which are approved and being used for several years in other countries may be waived off the clinical trials<sup>4</sup> by the Central Licensing Authority (CLA) i.e. Drug Controller General of India (DCGI) as per the New Drugs and Clinical Trial Rules, 2019 (NDs and CTs Rules, 2019) under special conditions. Earlier to this, applicants who wished to file drug product used to apply along with requisite fee. Preliminary evaluation of application was done; if it was acceptable then it underwent regulatory evaluation or the applicant had to re-file again.<sup>3,4</sup> After all the satisfactory data evaluation, applicant had to request for on-site facility inspection. If it was successful, then applicant was granted approval for manufacturing drug products. Data was compiled in the form of common technical document (CTD) prior to 2016. Recently CDSCO implemented the online Sugam portal for the marketing authorization application.<sup>5</sup> In recent times, stringent regulations regarding drugs and medical devices are becoming essential to achieve the aim of providing modern healthcare access to public at affordable rates. Government of India is striving towards 'affordable healthcare for all' and to achieve this goal, regulations for controlling drugs and medical devices are framed judiciously. Since April 2017, bioequivalence studies for BCS Class II and IV drugs are made compulsory in India to assure the quality of affordable medicines which will be made available to people.<sup>6</sup> A well achieved milestone towards this is the availability of medicines in Jan Aushadhi stores at much economic rates.<sup>7</sup> In addition, DCGI in June 2018 suggested segregation of generic medicines from branded ones and stocking them in a manner that is easily visible to consumers.<sup>8</sup> Biopharmaceutical Classification System (BCS) of drugs have been used as logical tool for design and testing of oral formulations, particularly tablets. Drug as per its solubility and permeability behaviour differ significantly in a way to produce designed therapeutic outcomes. Tablets of BCS II and IV drugs have been reported to show variation in formulation as well as pharmaceutical performance when manufactured by various industries.<sup>9,10</sup> Therefore, in the present study class I category drug with minimum variations in yielding therapeutic outcome and BCS II drug with marked variation in drug performance, in terms of bioavailability were selected for the study.

Levofloxacin, BCS I category drug, a synthetic fluoroquinolone antibacterial agent inhibits the super coiling activity of bacterial DNA gyrase, halting DNA replication. It has excellent antibacterial activity against many clinically significant pathogens such as *Pseudomonas aeruginosa* and *Escherichia coli*. Levofloxacin with 4-8 h half-life is known for rapid and almost complete absorption from the gastrointestinal tract (GIT), reaching peak plasma concentrations approximately 1–3 h after oral administration.<sup>11,12</sup>

BCS II type drug, cefuroxime is a broad-spectrum cephalosporin antibiotic resistant to beta-lactamase. It has excellent antimicrobial activity against *Micrococcus luteus* and *Kocuria rhizophila*. Cefuroxime, like penicillin, is a beta-lactam antibiotic that binds to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall and inhibits the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins wherein cefuroxime interferes with an autolysin inhibitor. After oral administration, cefuroxime is absorbed from the GIT and rapidly hydrolysed by non-specific esterase's in the intestinal mucosa and blood. It is subsequently distributed throughout the extracellular fluids in adults.<sup>13,14</sup>

The present study was aimed to compare the tablets having significant difference in retail prices of levofloxacin hemihydrate (LH) and cefuroxime axetil (CA) by using pharmacopoeial evaluation tests, *ex vivo* permeability studies and antimicrobial activity in order to establish similarity or difference between the quality and efficacy of tablets with different prices. This study will help in building public confidence and raising social awareness about affordable medicines.

## MATERIALS AND METHODS

### Materials

Levofloxacin hemihydrate (LH) and cefuroxime axetil (CA) were procured from Micro Labs, Bengaluru and Wockhardt Ltd., Aurangabad, respectively. The film coated tablets of different brands, LH high cost (LH-HC) tablet 500, LH medium cost (LH-MC) tablet 500 were purchased from local retail pharmacies in Pune, India. LH low cost (LH-LC) tablets 500 were obtained from Jan Aushadhi (JA) store, Pune, India. Film coated, CA high cost (CA-HC) tablet 250/500 and CA medium cost (CA-MC) tablet 250/500 and CA low cost (CA-LC) tablets 250/500 mg were purchased from local retail pharmacies and Jan Aushadhi (JA) store, Pune, India, respectively. Tablets with their details are mentioned in Table 1. Acetonitrile of HPLC grade was purchased

**Table 1: Tablets Samples Purchased From Market.**

	Film coated Tablet	Strength	Batch Number	Manufacturing Date	Expiry Date	Maximum Retail Price (Rs.) per tablet
Levofloxacin hemihydrate	LH-HC-500	500 mg	AEP 81339	11/2018	10/2021	8.48
	LH-MC-500	500 mg	ALD810A	9/2018	8/2019	8.48
	LH-LC-500	500 mg	GT171425	10/2017	09/2020	2.6
Cefuroxime axetil	CA-HC-250	250 mg	MA227	10/2018	9/2020	52.5
	CA-MC-250	250 mg	LOB870A	10/2018	09/2020	18.8
	CA-LC-250	250 mg	CT8044	05/2018	04/2021	5.6
	CA-HC-500	500 mg	MA529	05/2018	04/2020	94.1
	CA-MC-500	500 mg	LOC804A	04/2018	03/2020	32.66
	CA-LC-500	500 mg	GT171427	10/2017	09/2020	2.68

#LH, CA, HC, MC and LC stands for Levofloxacin hemihydrate, Cefuroxime axetil, high cost, medium cost and low cost respectively.

from Sigma Aldrich, India. All other chemical and reagents used were of analytical grade, purchased from Merck, India. Gram-negative bacteria *Escherichia coli* (ATCC-10536) and gram-positive bacteria *Micrococcus luteus* (ATCC-10786) were used as test micro-organisms for the antimicrobial study of LH and CA, respectively. Muller-Hinton agar was used for antimicrobial assay.

#### Development of standard curve

Drug standard curves were developed in various buffers (pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8) and water using UV-Vis spectrophotometer. Accurately weighed amount of drug (LH / CA) was dissolved in buffers or water, sonicated if necessary. Further dilutions were made using respective solvents to obtain stock and working standard solutions in the concentration range of 2 to 18 µg/ml for LH and 4 to 20 µg/ml for CA.<sup>15,16</sup> Absorbance maxima ( $\lambda_{max}$ ) were measured using UV-Visible spectrophotometer (JASCO-V630). The absorbance values of all working standard solutions were measured at their respective absorbance maxima. All the experiments were done in triplicates ( $n=3$ ). Linearity was established over the entire concentration range by plotting graph of absorbance versus corresponding concentrations. The data were statistically evaluated using linear regression analysis.

#### Biopharmaceutical classification system (BCS) solubility

The BCS solubility of a drug is determined by dissolving the highest unit dose of drug in 250 ml of aqueous media throughout the pH range 1.0 to 6.8. As the highest doses of LH and CA is 750 mg and 500 mg, respectively, the same were considered for this study. Accurately weighed drugs were added to above solvents, under continuous agitation for 24 h using Brunswick

scientific Excella incubator shaker at  $37 \pm 1^\circ\text{C}$ . Later the solution was filtered through 0.45 µ Whatman filter paper and suitable dilutions were made. Quantity of solubilised drug was determined using UV-Vis spectrophotometer at their respective  $\lambda_{max}$  ( $n=3$ ).<sup>17,18</sup>

#### Evaluation tests for tablets

##### Hardness

Six tablets of LH / CA (in respective strengths) were used for hardness testing using a Monsanto Hardness Tester.

##### Weight Variation

Randomly 20 film coated tablets of LH / CA (in respective strengths) were taken and weighed individually for calculating average weight. The deviation of individual weights from the average weight was determined as per Indian Pharmacopoeia (IP) 2018 procedure.<sup>19</sup>

##### Disintegration test

The disintegration test was performed on six units of LH / CA (in respective strengths) as per IP 2018 procedure. The disintegration time in water was measured using Electro lab DT1000 disintegration test apparatus at  $37 \pm 1^\circ\text{C}$ .<sup>19</sup>

##### Friability

LH / CA tablets equivalent to 6.5 g or nearest higher weight were considered and initial weight was recorded. Friability was performed using friability tester by rotating the respective tablets in drum for 100 rotations followed by dedusting and recording of final weight.<sup>19</sup> Percent friability was calculated using following equation

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

## Assay of LH and CA

### Preparation of test solution

For LH, 20 tablets were weighed and powdered using mortar pestle. Accurate quantity of powder containing 100 mg of levofloxacin was dispersed in 100 ml 0.1 M HCl followed by filtration and subsequent dilution with water. Randomly 10 tablets of CA were dispersed in 0.2 M ammonium dihydrogen orthophosphate with previously adjusted pH to 2.4 using orthophosphoric acid (10 ml per g of the stated content of cefuroxime). Sufficient methanol was immediately added to produce a solution containing the equivalent of 0.5 % w/v of cefuroxime and shaken vigorously. Obtained filtrate was further diluted with sufficient mobile phase to produce a solution containing 0.025 % w/v of CA.<sup>19</sup>

### Preparation of reference solution (RS)

A 0.1% w/v solution of LH RS was prepared by dissolving levofloxacin in 0.1M HCl. From above solution, 5 ml volume was withdrawn and diluted to 50 ml with water. 0.03 % w/v solution of CA RS was prepared in the mobile phase. The column used for levofloxacin and cefuroxime was RP-C<sub>18</sub> Column (250 x 4.6 mm, 5 μ) with methanol: 0.2M ammonium dihydrogen orthophosphate (38:62 % v/v) and 1M ammonium acetate: acetonitrile (85:15 % v/v), respectively as mobile phases. Injection volume (20 μl) was used at the flow rate of 1.2 ml/min (293 nm) and 1 ml/min (278 nm) for LH and CA, respectively.<sup>19</sup>

### In vitro dissolution test

Dissolution test was carried using 6 units of the respective dosage form as per IP 2018. The test was carried out using Electrolab Dissolution test apparatus (TDT-06L). As per IP, the dissolution media specified in individual monograph for LH and CA is 0.01 M HCl and 0.1 M HCl, respectively. Additionally, this study was also performed with pH 1.2, acetate buffer pH 4.5, phosphate buffer pH 6.8 and distilled water as dissolution medium in accordance with the USFDA Guidance for Industry<sup>19</sup> in Electrolab Dissolution test apparatus (Paddle type). Volume of media was 900 ml wherein 5 ml samples were withdrawn at 5, 10, 15, 30 and 45 min time points under sink conditions. RPM was maintained at 100 and 50 for LH and CA, respectively at 37±5°C. Acceptance criteria are not less than 70% of stated amount for both the drugs. After each time points, the aliquot was taken and filtered through 0.45 μ Whatman paper to remove the undissolved particles. Further dilutions were made and subjected to UV-Vis spectrometer for measuring the drug release at 293 nm and 281 nm, respectively.<sup>16,17,19-21</sup>

### Ex vivo permeation study

*Ex vivo* permeation study was performed using everted gut sac technique.<sup>21,22</sup> The freshly cut, goat gut was collected from local slaughter house, Pune and placed in a mixture of Krebs-Ringer phosphate solution and isopropyl alcohol (70:30 v/v). The gut was then washed with cold oxygenated saline solution and sectioned into 10 cm small portions. One side of the gut sac was tied using a thread. With the help of glass rod, gut sac was everted by sliding it over the opposite side so that the surface was inside out. Sticky matter was cleaned using cold Ringer's solution. Phosphate buffer saline pH 7.4 was filled in the gut sac and tied from the other end. This sac was placed in the flask of dissolution apparatus containing 900 ml phosphate buffer saline pH 7.4 at 37±1°C at the aeration rate of 1-2 bubbles per second. Later, LH and CA tablets were placed in the dissolution apparatus. This study was performed using same machine parameters followed for dissolution test. Samples were withdrawn at single time point of 3 h from the dissolution flask and gut sac. Further drug release and amount permeated was calculated using UV-Vis spectrophotometer at absorbance maxima ( $\lambda_{max}$ ) 293 nm and 281 nm, respectively for LH and CA. This procedure was followed to assess the simultaneous permeation of the drug post tablet disintegration and dissolution.<sup>23,24</sup>

### Microbial assay

Microbial assay was performed in autoclaved Müller-Hinton Agar media by well diffusion method.<sup>21,25</sup> Autoclaved media was poured in the sterile Petri plates aseptically and kept for solidification. Post solidification, test cultures were spread on the media with the help of glass spreader. Subsequently, wells were drilled with the help of sterile cork borer. Antimicrobial study was performed at 5, 10, 15 mg/ml LH and 50, 100, 150 μg/ml CA concentrations.<sup>10,12</sup> Various drug concentrations of LH and CA products were added in respective, labeled wells, aseptically. After diffusion, these inoculated and supplemented plates were incubated at 35±2°C aerobically for 24 h. Following incubation, the area of inhibition (mm<sup>2</sup>) around the well was calculated and compared using a concentration versus area of inhibition graph.

## RESULTS AND DISCUSSION

LH and CA were selected as prototype drugs from BCS class I and class II categories, respectively for present study. From market survey, it was found that



comparatively very less number of tablet type products are available in market which contain LH and CA. Price variation for LH products was comparatively less as it comes under National Pharmaceutical Pricing Authority (NPPA).<sup>22,23</sup> However, for CA products, significant cost difference was found. Thus, we selected LH and CA tablets manufactured by different companies with cost difference viz. high cost (LH-HC) tablets 500, (CA-HC) tablets 250/500; Medium cost (LH-MC) tablet 500, (CA-MC) tablet 250/500 from retail pharmacies and low cost (LH-LC) tablets 500, (CA-LC) tablets 250/500 mg from Jan Aushadhi (JA) stores, respectively for our research work.

### UV spectrometric calibration curve

The calibration curve was developed in four media, as recommended by USFDA guidance<sup>20</sup> for routine drug analysis in dissolution study as well as other evaluation tests such as solubility and permeation study in the range of 2-18 µg/ml and 4-20 µg/ml for LH and CA, respectively. The data were statistically evaluated using linear regression analysis with a regression coefficient 0.99.

**Table 2: BCS solubility study of LH and CA in different pH media (n=3).**

Medium Strength	Solubility (mg/250 ml)*	
	Levofloxacin hemihydrate (LH) 750 mg	Cefuroxime axetil (CA) 500 mg
Water	651.70±0.08	76.80±0.085
0.1 M HCl (pH 1.2)	673.10±0.038	107.00±0.38
Acetate Buffer (pH 4.5)	676.80±0.24	274.30±0.24
Phosphate Buffer (pH 6.8)	692.80±0.08	303.00±0.08

# BCS stands for Biopharmaceutical Classification System.

\*Results are expressed as mean ± SD, where n=3. SD: Standard deviation

### BCS solubility

As per USFDA guidance, solubility of a drug substance is considered in the volume less than or equal to 250 mL.<sup>20</sup> Volume of 250 ml is equal to 8 ounces as it is considered that tablet is taken with 1 glass of water, equivalent to 8 ounces.

For BCS solubility studies of LH and CA, 750 mg and 500 mg were the highest strengths, respectively performed using 250 ml in various media ranging from pH 1.0 to 6.8. Highest dose solubility (more than 90% of drug) for LH was found to be 692 mg in 250 mL phosphate 6.8 buffer (Table 2). Data revealed its high solubility in pH 4.5 and pH 6.8 when compared to water and pH 1.2. Almost 50% of CA was solubilised at higher pH whereas less solubilisation was observed at lower pH (Table 2). LH belongs to BCS class I (high solubility) category.<sup>24,26</sup> CA belongs to BCS class II (low solubility) category.<sup>27</sup> For CA, variation in solubility was observed reflecting pH dependant solubility.

### Evaluation tests for tablets

As summarized in Table 3, all the tablets tested were within the limits specified for the uniformity of weight by IP. However, they exhibited different hardness which is known to impact disintegration and dissolution behaviour. When evaluated, the effect of hardness was observed as the tablet with low hardness exhibited shorter disintegration time and vice versa. Yet, all the tablets disintegrated within the time specified by the IP, thereby passing the test.<sup>19</sup>

### Assay of tablets by HPLC method

As per IP, tablet should contain not less than 90 % and not more than 110 % of stated amount of drug (LH as well as CA).<sup>19</sup> The drug content determined using RP-HPLC method revealed the compliance within IP

**Table 3: Pharmacopoeial Evaluation of LH and CA Tablets.**

Tablet	Weight variation* (mg)	Thickness/width* (mm)		Hardness* (kg/cm <sup>2</sup> )	Friability* (%)	Disintegration time* (min)	Drug content* (%)
LH- HC -500	686±34.3	5.00±0.069	17.01±0.009	11±0.81	0.01±0.0029	3.34±0.055	99.1±0.02
LH-MC-500	695±34.75	4.63±0.028	18.31±0.026	9±0.47	0.02±0.0036	3.8±0.047	98.1±0.036
LH-LC -500	942±47.1	5.67±0.255	20.03±0.024	7±0.47	0.04±0.0039	3.1±0.013	98.2±0.025
CA-HC -500	924.25±46.21	6.32±0.020	18.03±0.023	10±0.47	0.01±0.0021	1.36±0.023	99.98±0.02
CA-MC -500	943.2±47.16	4.89±0.020	18.25±0.018	11±0.47	0.01±0.0032	3.2±0.041	97.41±0.01
CA-LC -500	974.5±48.71	5.26±0.024	21.02±0.012	12±0.47	0.04±0.0023	5.6±0.032	95.52±0.04
CA-HC -250	462±23.1	5.27±0.047	15.11±0.061	7±0.47	0.02±0.0012	1.5±0.054	99.93±0.01
CA-MC -250	470±23.5	4.73±0.066	14.70±0.083	8±0.47	0.01±0.0042	2±0.012	97.41±0.02
CA-LC -250	630±31.5	5.16±0.065	16.49±0.066	10±0.47	0.03±0.0026	2.3±0.066	97.27±0.066

# LH, CA, HC, MC and LC stands for Levofloxacin hemihydrate, Cefuroxime axetil, high cost, medium cost and low cost, respectively.

\*Results are expressed as mean ± SD, where n=3. SD: Standard deviation

limits. Hence all the tablets passed the limits specified in IP as per Table 3.

### In vitro dissolution study

All the tablets were found to release more than 70 % of total drug content which complies with the IP limits for dissolution test as specified in individual monographs of LH and CA.<sup>19</sup> Additionally, dissolution testing was performed as per USFDA guidance (multimedia dissolution test).<sup>20</sup>

The data revealed pH independent drug release for LH tablets which can be attributed to its pH independent high solubility. The dissolution graphs for LH 500 are shown in Figure 1 and CA 250 and 500 in Figures 2 and 3, respectively. Similarity factor ( $f_2$ ) calculated for comparing the dissolution profiles of medium cost and low-cost tablets with high cost tablets, revealed the similarity of drug release profile amongst all (Table 4). Low-cost tablets exhibited slight lower release than the medium cost and high cost tablets however; the difference was not significant ( $p > 0.05$ ). All low-cost tablets complied with the IP limits.

### Ex vivo permeation

Bioavailability is commonly known as extent and rate at which drug reaches systemic circulation.<sup>26</sup> Intestinal permeability is principal determinant of drug absorption post oral administration. Transport across the intestinal

barrier is a prerequisite for clinical effects of most drugs and intestinal permeability is used for classifying drugs in the biopharmaceutical classification system (BCS). Numerous methods have been used to evaluate intestinal absorption of drugs. *Ex vivo* and *in situ* models in small animals are also widely used when there is a good agreement between intestinal permeability. *Ex vivo* methods like everted gut sac techniques provide theoretical means of estimating human intestine absorption.<sup>28</sup> For LH, amount of dissolved and permeated drug was same. In case of CA, there was difference in the amount of dissolved and permeated drug (Table 5). This was in accordance to their respective BCS class. LH tablets revealed the identical correlation between dissolution and permeation studies which underlined the solubility dependent drug absorption for all brands of LH irrespective of their price. As CA belongs to BCS class II, various brands of CA were unable to illustrate solubility dependent drug absorption.

### Microbial assay

Microbial assay of an antibiotic is the key measure of its effectiveness.<sup>12,25</sup> Zone of inhibition around the well is directly proportional to the effectiveness of drug in a specific test microbial strain. The data revealed that effectiveness of both drugs is concentration dependant. Also, there was no significant difference observed for the tablets of various brands when data was statistically

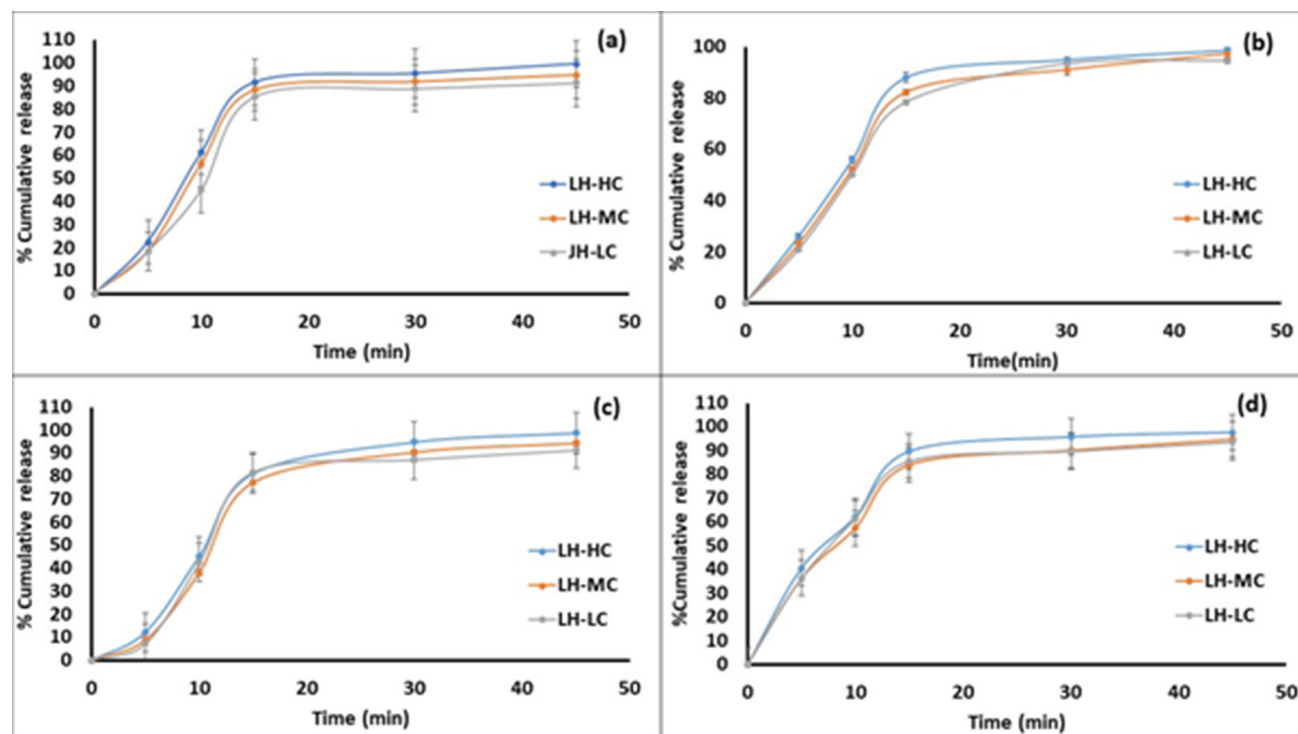


Figure 1: Dissolution profiles of different LH 500 brands in (a) water, (b) 0.01M HCl (c) acetate buffer pH 4.5 and (d) phosphate buffer pH 6.8.

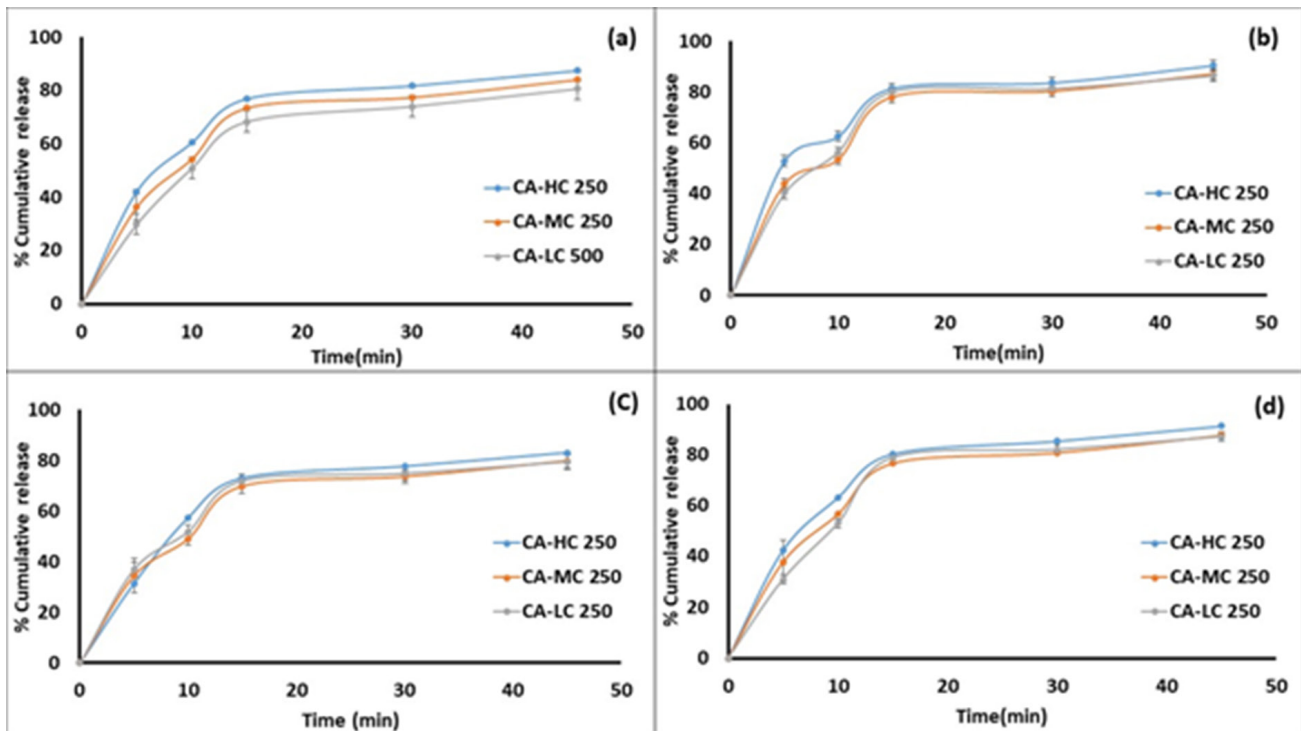


Figure 2: Dissolution profiles of different CA 250 brands in (a) water, (b) 0.1M HCl (c) acetate buffer pH 4.5 and (d) phosphate buffer pH 6.8.

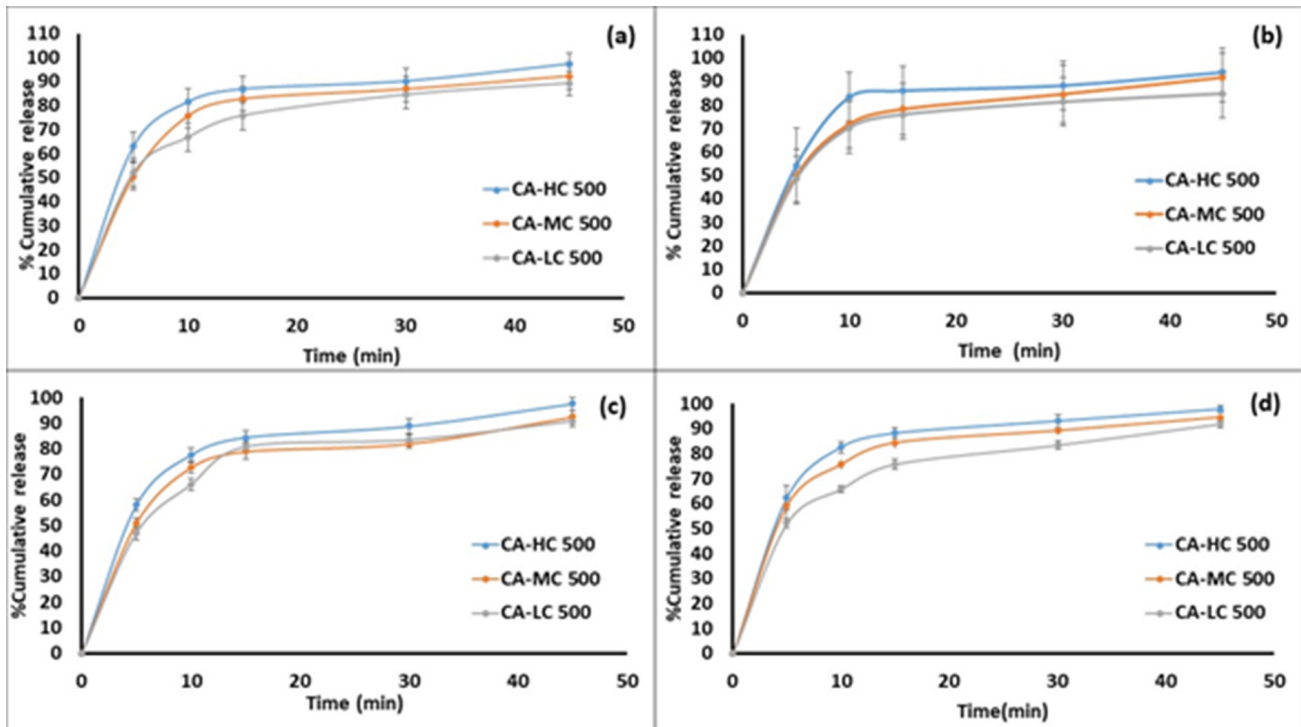


Figure 3: Dissolution profiles of different CA 500 brands in (a) water, (b) 0.1M HCl (c) acetate buffer pH 4.5 and (d) phosphate buffer pH 6.8.

**Table 4: Similarity Factor for LH and CA Tablets Dissolution Test.**

Tablet	Label amount mg/ tab	Media					
		0.1 M / 0.01 M HCl (CA / LH)		Acetate buffer pH 4.5		Phosphate buffer pH 6.8	
		f2 value	Similarity	f2 value	Similarity	f2 value	Similarity
LH-MC - 500	500 mg	72.09	Yes	67.43	Yes	67.58	Yes
LH-LC - 500	500 mg	63.46	Yes	65.01	Yes	69.84	Yes
CA-MC -500	500 mg	59.84	Yes	62.98	Yes	68.73	Yes
CA-MC -250	250 mg	61.41	Yes	67.45	Yes	68.25	Yes
CA-LC -500	500 mg	52.93	Yes	55.74	Yes	52.65	Yes
CA-LC - 250	250 mg	60.48	Yes	70.77	Yes	58.91	Yes

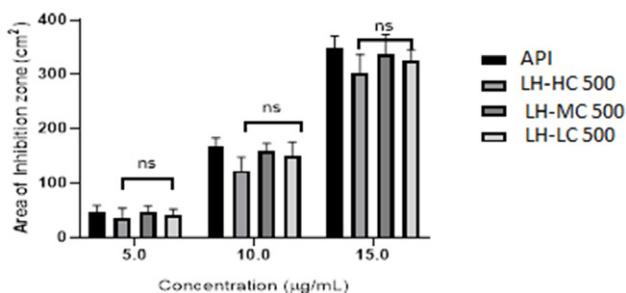
# f2 stands for similarity factor.

**Table 5: Permeation of both LH and CA Tablets in phosphate buffer pH 7.4.**

Tablet	%Drug release*	%Drug permeated*
API- LH	99.80±0.17	98.2±0.34
LH-HC -500	97.40±0.29	96.30 ±0.25
LH-MC -500	96.70±0.46	95.50 ±0.22
LH-LC -500	96.90±0.36	95.80 ±0.35
API – CA	70.01 ±0.21	92.40±0.32
CA-HC -500	75.13 ±0.32	90.40±0.42
CA-MC -500	73.22 ±0.46	89.30±0.33
CA-LC -500	72.50 ±0.32	88.10±0.25
CA-HC -250	74.44 ±0.22	91.30±0.37
CA-MC -250	72.23 ±0.37	89.40±0.27
CA-LC -250	71.32 ±0.29	87.90±0.40

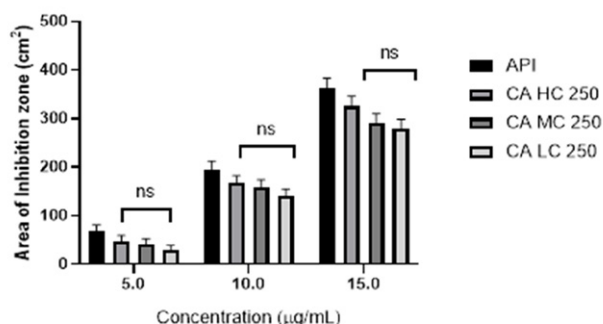
# API, LH, CA, HC, MC and LC stands for active pharmaceutical ingredient, levofloxacin hemihydrate, cefuroxime axetil, high cost, medium cost and low cost, respectively.

\*Results are expressed as mean ± SD, where n=3. SD: Standard deviation

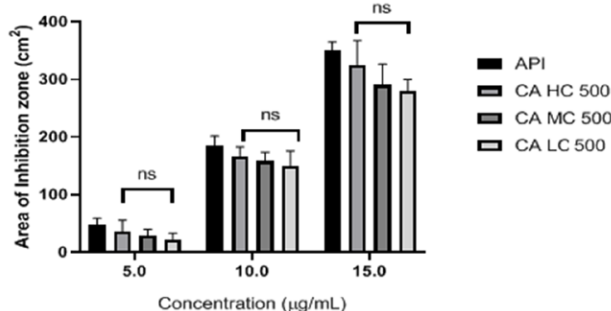


**Figure 4: Microbial assay of API and LH 500 tablets against Escherichia coli (ATCC-10536). [ns = non-significant]**

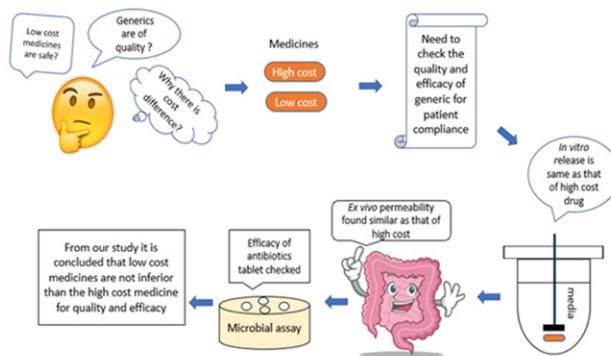
analysed using non-parametric Students *t*-test ( $p > 0.05$ ). This can be attributed to the inherent antimicrobial property of drug which is independent of tablet manufacturers, especially when all the formulations are pharmaceutically equivalent. Figures 4-6 represent the relationship between the zone of inhibition and concentration of drug solutions for LH tablets (500 mg), CA (250 mg and 500 mg) tablets,



**Figure 5: Microbial assay of API and CA 250 tablets against Micrococcus luteus (ATCC-10786). [ns = non-significant]**



**Figure 6: Microbial assay of API and CA 500 tablets against Micrococcus luteus (ATCC-10786). [ns = non-significant]**



**Figure 7: Representative protocol for scrutinizing various antibiotic tablet brands with cost difference.**



respectively along with their respective API. As compared to API, LH as well as CA tablets showed less inhibition as the excipients control the release of active moiety from the tablets.<sup>12,14</sup>

In brief, it was revealed that for BCS class I and II antibiotic tablets, a protocol depicted in Figure 7 can be useful to compare the quality as well as efficacy of various drug brands with different cost. This protocol will be useful tool for assessing low cost alternatives of essential drugs which will assist the regulatory agencies to monitor their manufacturing facility prior to licensing. Additionally, this study helps to build confidence about affordable medicines in general public as well as physicians considering their pharmaceutical quality and safety in patients. However, this study is limited to laboratory testing of few prototype drugs and dosage forms of existing brands. Additionally, the cGMP practices employed during manufacture, transport and storage of medicines needs to be considered.

## CONCLUSION

A common mind-set regarding low cost medicines is that they have compromised quality whereas higher is the price of medicine, better is its quality and efficacy like other conventional products. In this study, we have compared various products of the same drug with varied price range. It was revealed that there is no significant difference between the efficacy of high-cost, medium-cost and economical products of medicines procured from Jan Aushadhi store, a social initiative by Government of India. Quality check for the pharmaceutical evaluation of tablets (IP) and *in vitro* dissolution along with efficacy check via *ex vivo* permeability and antimicrobial studies proved that there is no discrepancy between quality as well as efficacy of low cost and other brand tablets. This would be an infallible, rapid protocol, valuable in bringing quality generics in market prior to the clinical trials which suffer due to time lag and legal hassles. This would accelerate the public access and improve perception to the essential drugs at affordable cost, supporting the initiative undertaken by government in the form of Jan Aushadhi.

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## CONFLICT OF INTEREST

The authors declare no Conflict of interest.

## ABBREVIATIONS

**WHO:** World Health Organization; **CDSCO:** Central Drug Standard Control Organization; **CLA:** Central Licensing Authority; **DCGI:** Drug Controller General of India; **CTD:** Common Technical Document; **BCS:** Biopharmaceutical Classification System; **GIT:** Gastrointestinal Tract; **LH:** Levofloxacin Hemihydrate; **CA:** Cefuroxime Axetil; **JA:** Jan Aushadhi; **HC:** High Cost; **MC:** Medium Cost; **LC:** Low Cost; **ATCC:** American Type Culture Collection; **IP:** Indian Pharmacopoeia; **RS:** Reference Solution; **NPPA:** National Pharmaceutical Pricing Authority; **GMP:** Good Manufacturing Practices.

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### PICTORIAL ABSTRACT



### SUMMARY

Global and national health agencies promote accessibility of affordable medicines to the masses. The Government of India has initiated the Jan Aushadhi stores to offer quality medicines at economic price. The biggest challenge in this attempt is improving the public perception by comparing the quality and efficacy of low-cost medicines. When levofloxacin hemihydrate (LH) and cefuroxime axetil (CA) tablets with price difference including the products from Jan Aushadhi stores were evaluated using pharmacopoeial evaluation tests, *ex vivo* permeability study and antimicrobial activity, no significant difference between the quality and efficacy of tablets was observed. Thus, the affordable products available in medical stores, especially Jan Aushadhi stores are at par with the branded products and should be prescribed / administered to the patients.

### About Authors



**Dr. Atmaram Pawar** is presently serving as Principal (I/C) and Professor of Pharmaceutics at Poona College of Pharmacy, Pune. He has 04 patent applications, 101 international & 32 national peer reviewed research papers with Google Scholar *h*-index 33, Scopus listed 99 publications, *i*-10 index 70. Dr. Pawar has guided 10 Ph.D students. He has published 03 books in Indian languages, published more than 70 articles in leading newspapers for promoting pharmacy profession in society. He is a recipient of 11 prestigious international and national awards.



**Mahesh Chainpure** has completed his M.Pharm in Drug Regulatory Affairs from Poona College of Pharmacy, Pune. Currently, he is working in the area of Regulatory Affairs Associate at Parexel, Bengaluru.



**Dr. Vividha Dhapte-Pawar** is currently working as Associate Professor of Pharmaceutics at Poona College of Pharmacy, Pune. She has pursued her B.Pharm, M.Pharm and Ph.D from Bharati Vidyapeeth University with Gold Medals. She has 02 patent applications, 30 international peer reviewed papers, 06 international book chapters and 1 book. She has been a proud recipient of 4 Gold Medals at the B.V. Patel Trust National Essay Competition.

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