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EXTENDED RELEASE TABLET FORMULATION OF A MACROLIDE ANTIBIOTIC

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ABSTRACT

Clarithromycin is a macrolide antibiotic. The objective is to design the extended release tablet of Clarithromycin which will exhibit comparative in-vitro and in-vivo drug release profile as that of marketed product. The designed formulation utilizes a combination of Hydroxypropyl Methylcellulose 5 cps and 15 cps as rate controlling polymers for drug release. The process is a wet granulation process using FBP. The finalized extended release tablet showed comparative in vitro and in vivo drug release profile against the marketed product BIAXIN XL FILM TAB®. Also the physico-chemical properties of the finalized extended release tablets of Clarithromycin was found to be stable for 3 months at of 40°C / 75% RH.

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INTRODUCTION

Clarithromycin is a macrolide antibiotic[1]. Clarithromycin is a white to off-white crystalline powder[2]. It is soluble in acetone, slightly soluble in methanol, ethanol and acetonitrile and practically insoluble in water[3]. Clarithromycin extended-release tablets provide extended absorption of clarithromycin from the gastrointestinal tract after oral administration[4]. Relative to an equal daily dose of immediate-release clarithromycin tablets, clarithromycin extended-release tablets provide lower and later steady-state peak plasma concentrations but equivalent 24 hour AUC's for both clarithromycin and its microbiologically active metabolite, 14-OH clarithromycin[5-7]. While the extent of formation of 14-OH clarithromycin following administration is not affected by food, administration under fasting conditions is associated with approximately 30% lower clarithromycin AUC relative to administration with food. Therefore the extended-release tablets should be taken with food. ER tablets of Clarithromycin are indicated for the treatment of adults with mild to moderate Acute maxillary sinusitis, Acute bacterial exacerbation of chronic bronchitis and Community-Acquired pneumonia[8-11].

OBJECTIVE

The objective is to develop an extended release dosage form of Clarithromycin which would be comparable to the marketed product, BIAXIN XL FILM TAB® with respect to physico-chemical properties and drug release characteristics.

JUSTIFICATION OF RESEARCH

Most of the available research reported uses costly polymers, organic solvents and complex manufacturing process viz Hot melt extrusion, Ion-resin complexation etc to design the extended-release tablets of Clarithromycin. The present research will focus to design a process which is environment friendly simple granulation process by which the cost effectiveness is very much realisable.

MATERIALS AND METHODS

EXCIPIENTS & REAGENTS

Clarithromycin from Ranbaxy Labs; Hypromellose (Methocel E5), Hypromellose (Methocel E15) and Hypromellose (Methocel K100M CR) from Dow; Sodium Alginate Low Viscosity grade (Keltone LVCR) and Sodium Alginate High Viscosity grade (Keltone HVCR) from FMC Biopolymer; Ethyl Cellulose (Ethocel 45 Premium) from Colorcon; Colloidal Silicon Dioxide (Cab-O-Sil) from Cabot Sanmar; Stearic Acid Triple Compressed from J.T. Baker; Glycerl Behenate (Compritol ATO 888) from Gattefosse; Methacrlic Acid Copolymer (Eudragit L100) from Evonik; Talc (Luzenac Talc UM) from Imerys; Lactose Monohydrate (Pharmatose 200M) from DMV Fonterra Excipients; Magnesium Stearate Vegetable grade (Tablube) from Nitika Chemicals; Opadry II White 85F18422 from Colorcon. Ortho Phosphoric Acid, Sodium Hydroxide Pellets, Potassium Dihydrogen Phosphate and Potassium Hydroxide from Merck; Acetonitrile from J.T. Baker; MilliQ Water was used for Analytical Purpose.

EQUIPMENTS & INSTRUMENTS

Vibrosifter of Gansons; FBP of Pam Glatt; 16 Station Tablet Press of Cadmach; Hardness Tester of Erweka; Disintegration Test Apparatus of Electrolab; Vernier Caliper of Mitutoyo; Friabilator of Electrolab; Electromagnetic Sieve Shaker of Electrolab; Tap Density Testing Apparatus of Electrolab; Bottle Sealing Machine of Sigma Flex; Double Cone Blender of Sams Technomech; LOD Mositure Analyzer of Ohaus; Comminuting Mill equipped with 0.8 mm Screen of Cadmach; 40°C / 75% RH Stability Chamber of Thermolab; UV Visible Spectrophotometer of Perkin Elmer; 20.8 mm X 9.0 mm Oval Shaped Concave Plain Punch Tooling of ACG PAM; Auto Coater 12" Coating Pan of YenChen; Weighing Machine PS6000/C/1 of LCGC RADWAG; pH Meter H12215 of Hanna Instruments; Lab Stirrer RQ-126D of Remi; Dissolution Apparatus of Electrolab; Column Kromasil C18 4.6 x 100 mm, 3.5 µm particle size of Akzo Nobel.

METHOD OF ANALYSIS

Compendia method was followed for the determination of Assay, Blend Uniformity, Uniformity of Dosage Units and Dissolution as the drug and drug product is official in USP.

EXPERIMENTATION

MARKETED PRODUCT CHARACTERIZATION

Marketed product, BIAXIN XL FILMTAB® was characterized with respect to Weight, Thickness, Diameter, Dissolution Profile and Packaging configuration.

API CHARACTERIZATION

Clarithromycin was characterized with respect to Description, Form, Bulk Density, Tapped Density, Compressibility Index, Hausner Ratio, Loss on Drying and Particle Size Distribution.

DRUG-EXCIPIENT COMPATIBILITY STUDY

The possibility of drug-excipient interaction was investigated by HPLC analysis. Drug excipient compatibility study was performed with excipients mentioned above (See 'Excipients & Reagents'). Study was conducted by preparing homogenous mixture of excipient with drug filled in glass vials were exposed to 40 ± 2°C / 75 ± 5% RH and 60°C for 4 weeks and 2 weeks respectively. Samples were analysed for Assay, Total Impurity and Water By Kf.

FORMULATION

The ingredients listed in the Intragranular part of Table 1 were sifted through #20 ASTM sieve. The sifted materials were charged in FBP and were granulated with Purified water. The dried granulated mass was milled through comminuting mill fitted with 0.8 mm screen at high speed knives forward configuration. The milled granules were blended together in a Double Cone Blender at 15 RPM for 2 minutes. The extra granular materials except lubricant was sifted through #20 ASTM sieve and blended along with blended granules of intragranular part in a Double Cone Blender at 15 RPM for 15 minutes. Each lubricant was sifted through #40 ASTM sieve and blended with the blended materials in a Double Cone Blender at 15 RPM for 5 minutes each. The blend thus prepared was compressed into tablets using 20.8 mm X 9.0 mm Oval Shaped Concave D type Plain Punch Tooling in a 16 Station Single Rotary Tablet Press at 25 RPM. Tablets thus prepared were coated in a 12" coating pan.

The Fluid Bed Granulation parameters are as follows,

Air inlet temperature	: 40 °C ± 10 °C
Mixing Time	: 5 minutes
Shaking Mode	: Auto
Spraying Mode	: Auto
Air Outlet Damper Pressure	: 1 to 3 bar
Purified Water Spray Rate	: 80 ± 40 g/min
Atomization air pressure	: 4 ± 2 bar
Number of Spray Gun	: 1
Spray Nozzle	: 1.2 mm
Filter Shaking Duration	: 5 ± 1 seconds
Filter Shaking Interval	: 2 ± 1 minutes
LOD of dried granules	: NMT 2.0%

The Tablet coating parameters are as follows,

Inlet Air Temperature	: 50° ± 10°C
Pan Speed	: 3 to 10 RPM
Suspension Spray Rate	: 25 ± 15 g/min/gun
Atomized Air Pressure	: 4 ± 2 bar

Gun Distance From Tablet Bed: NMT 12 cm

EVALUATION

The blend was characterized with respect to LOD, Repose Angle, Bulk / Tapped Density, Hausner Ratio and PSD. Prepared Tablets were characterized with respect to Weight, Thickness, Hardness, Friability and Dissolution Profile. In case of dissolution, method followed was USP recommended dissolution method Test 4, USP-II (Paddle), 50 RPM, 900 mL, pH 6.0 ± 0.1 Phosphate Buffer Time: 2, 4, 8, & 12 hours. Specification: Not more than 25%, between 20% and 40%, between 45% and 75% and not less than 80% at the end of 2, 4, 8 and 12 hours respectively.

STABILITY STUDY

The finalized formulation was subjected to accelerated stability study at 40±2°C / 75±5% RH. 60 Tablets were packed in 120 CC HDPE bottle with 38 mm Child Resistant Cap and induction sealed. Description, Water Content, Assay, Related Substances and Dissolution were studied during stability.

IN-VIVO STUDY

An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, two-way crossover, bioequivalence study of Clarithromycin 500 mg Extended Release Tablets with that of BIAXIN XL FILM TAB® was conducted in 12 healthy adult human subjects under fasting and fed conditions. The study protocol was prepared and approval from Independent Ethical Committee – The Ethical Jury, Chennai was obtained. The studies were conducted in compliance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization's Good Clinical Practices guidelines and the guidelines of Indian Council of Medical Research for Biomedical Research on Human Subjects and Good Clinical Practices for Clinical Research in India. Study subjects were screened and enrolled for the study. Enrolled subjects were housed in the clinical facility for 11 hours prior to drug administration until 36 hours post dose for both the periods. In case of study under fasting condition, after overnight fasting of at least 10 hours, a single oral dose of either test or reference product was administered to the subjects in sitting posture with about 240 mL of water. In case of study under fed condition, after overnight fasting of at least 10 hours, subjects were served standard high-fat, high-calorie breakfast 30 minutes prior to administration of investigational product. After providing a high-fat, high-calorie breakfast, a single oral dose of either test or reference product was administered to the subjects in sitting posture with about 240 mL of water. The pre-dose 0 hour blood sample was collected before dosing and post dose samples were collected at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, 14, 16, 20, 24, 30 and 36 hours. Subjects were provided standard diet and continuously monitored for well-being and safety throughout the study.

The concentration of Clarithromycin in plasma samples were analysed using validated analytical method. Pharmacokinetic and statistical analyses were performed on obtained drug concentration data. Healthy, willing human volunteers between 18 and 45 years were selected on the basis of medical history, physical examination (including but may not be limited to an evaluation of the cardiovascular, gastrointestinal, respiratory and central nervous systems) vital sign assessments, 12-lead electrocardiogram (ECG), X-ray, and clinical laboratory assessments, urine screen for drugs of abuse and alcohol breath test. Informed consent was obtained from the subjects after explaining the nature and purpose of the study. Pharmacokinetic analysis was performed using WinNonlin® software version: 5.3 of Pharsight Corporation, USA for the following pharmacokinetic parameters Cmax, AUC0-t, AUC0-∞, Tmax, Kel, , t½ , Kel_Lower, Kel_Upper and AUC_%Extrap_obs. Analysis of variance (ANOVA) consistent with two one-sided test for bioequivalence, ratio analysis and 90% confidence intervals for ratio of least square mean of Ln-transformed data of Cmax, AUC0-t and AUC0-∞ for test and reference products were calculated by using SAS® statistical software version 9.1.3 from SAS Institute Inc, USA. For Clarithromycin, the 90% confidence interval of the relative mean Cmax, AUC0-t and AUC0-∞ of the test and reference product should be between 80.00% and 125.00% for log-transformed data.

RESULTS AND DISCUSSION

MARKETED PRODUCT CHARACTERIZATION

Details of marketed product characteristics were provided in Table 2. Based on the details the design was done for the developed product.

API CHARACTERIZATION

Details of API characterization were provided in Table 3. The wet granulation process was selected based on the API characteristics.

DRUG-EXCIPIENT COMPATIBILITY STUDY

Drug Excipient compatibility data shown in Table 4, suggests that both the temperature and moisture doesn't affect the stability of mixture indicating compatibility of drug with excipients studied.

FORMULATION

The characterization study for blend, tablets and coated tablets were done and is summarized in Table 5. For the prototype Batches A to E, the granulation, drying, milling, prelubrication and lubrication blending time were kept constant. The blend prepared was compressed with uniform hardness into tablets. The prepared tablets were then coated and the dissolution profile of the tablets was compared to the marketed product. Batch E showed comparative dissolution profile with that of Marketed Product and also complied with USP recommended dissolution method Test 4 in monograph of Clarithromycin Extended-Release Tablets. In Batch E, process parameters of milling, blending, and compression were optimized and finalized.

MILLING OPTIMIZATION

The dried granules were milled through Comminuting mill using 0.5 mm, 0.7 mm, 0.8 mm and 1 mm at fast speed, knife forward configuration. The flow property of milled granules through 0.5 mm and 0.7 mm were marginal, but the dissolution profile was comparable to the marketed product . Based on the dissolution results provided in Table 6, milling through 0.8 mm screen was finalized.

PRELUBRICATION BLENDING TIME OPTIMIZATION

The intragranular milled materials are blended with extra granular ingredients (except Lubricant) in a Double Cone Blender at 15 RPM for 10 minutes, 15 minutes and 20 minutes. At each time point, blend uniformity samples were collected in duplicate at 10 different locations in Double Cone Blender and submitted for analysis. The details are shown in Table 7. Based on the data, Prelubrication blending time in Double Cone Blender was fixed for 15 minutes.

MACHINE SPEED STUDY - TABLETTING

The final blend was compressed at different turret speed of 10 RPM, 25 RPM and 32 RPM. The tablets were collected and checked for weight variation and content uniformity. The details are provided in Table 8. Irrespective of machine speed, the weight variation and the content uniformity of the tablets compressed were within the USP limits.

HARDNESS STUDY - TABLETTING

The final blend was compressed at 3 different hardness. The tablets were collected and checked for Hardness variation, Thickness variation, Friability and Dissolution. The details are provided in Table 9. Hardness of 18-32 kP was finalized. At hardness of more than 35 kP, there is a reduction in drug release profile at 12^{th} hour time point and is not meeting the USP specifications.

DISSOLUTION PROFILE COMPARISON – INVITRO DRUG RELEASE

The finalized extended release formulation of Clarithromycin was characterized with respect to drug release rate & mechanism and linearity – Correlation coefficient. Dissolution profile and similarity & difference factor of prepared extended release tablets of Clarithromycin was comparable to the marketed product. The details are shown in Table 10, Table 11 and Figure 1. For dissolution profile comparison, model independent approach using a similarity factor comprising difference factor f1 and similarity factor f2 was calculated and the details are provided in Table 11. From the data it can be ensured sameness or equivalence of both Test and marketed product. The drug release rate and linearity – correlation coefficient was determined for both Test and marketed product. The details are shown in Figure 2 and Figure 3. From Figure 2 and Figure 3, it is clear that the there is no significant difference in the linearity (R^2 - Correlation Coefficient) as well as the drug release rate (m – Slope of the equation) hence both Test and Marketed products are comparable to each other. Following the drug release rate and linearity determination, mathematical models were constructed to determine the kinetics of drug release from dosage form and will help to optimize the design of the drug delivery system with programmed release rate characteristics. Model dependent methods like Zero Order, First Order, Higuchi and Korsmeyer-Peppas were applied for both marketed product and test product. See Table 12. Linearity was determined based on which the model was identified for the kinetics of drug release. From the graphical plots, it is clear that both the marketed product and the test product follows Zero Order model, indicating drug dissolution from dosage form that do not disaggregate and release the drug slowly with no change in area and equilibrium conditions. Matrix tablets with low soluble drugs and Osmotic Systems follows Zero order drug release profile and it is ideal to achieve a pharmacologically prolonged action.

TABLES AND FIGURES

TABLE 1. FORMULATION OF PROTOTYPES BATCH NO. A, B, C, D & E.

S.No	Ingredients	mg /tablet				
		A	**B**	**C**	**D**	**E**
1	Clarithromycin	508.0*	508.0*	508.0*	508.0*	508.0*
2	Hypromellose 15 cps (Methocel E15 Premium LV)	287.0	287.0	295.0	165.0	210.0
3	Hypromellose 5 cps (Methocel E5 Premium LV)	165.0	116.0	165.0	295.0	273.0
4	Purified Water, USP (Granulating Fluid)	QS	QS	QS	QS	QS
Total Intragranular Part		951.9	911.0	968.0	968.0	991.0
5	Hypromellose 15 cps (Methocel E15 Premium LV)	190.0	239.0	-	-	-
6	Hypromellose 5 cps (Methocel E5 Premium LV)	-	-	190.0	190.0	167.0
7	Talc (Luzenac Talc UM)	-	-	6.0	6.0	6.0
8	Magnesium Stearate (Non-Bovine Grade Tablube)	7.0	7.0	12.0	12.0	12.0
Total Extragranular Part		197.0	246.0	208.0	208.0	185.0
ER Core Tablet Weight		1157.0	1157.0	1176.0	1176.0	1176.0
Coating						
9	Opadry II White 85F18422	40.5	40.5	41.2	41.2	41.2
10	Purified Water	QS	QS	QS	QS	QS
Coated ER Tablet Weight		1197.5	1197.5	1217.2	1217.2	1217.2

*Based on Assay correction.

Note: The quantity of purified water for granulation is 80% of total intragranular ingredients and for coating is 20% w/w of coating ingredient.

Table 2 CHARACTERIZATION OF BIAXIN XL FILM TAB®.

Description	**Yellow oval film-coated tablets debossed with the Abbott logo on one side and a two- letter Abbo-Code KJ on the opposite side.**
Dimension (mm)	20.8 (Length) X 9.0 (Widh)
Weight range (mg)	1009 to 1032
Thickness range (mm)	8.15 – 8.23
Hardness range (kP)	14.6 – 17.3
Loss On Drying (%) (105°C – Auto mode)	1.68
Inactive Ingredient Details	Cellulosic polymers, Lactose monohydrate, Magnesium Stearate,Propylene glycol, Sorbic acid, Sorbitan monooleate, Talc, Titanium dioxide, D&C Yellow No.10 and Vanillin
Packaging Configuration	Bottle of 60 Tablets. White Rectangular Shaped HDPE Bottle. Child Resistant Closure Induction Sealed.
Dissolution (6 Units) Time (hrs) Vs Mean % Drug Dissolved	2 hours – 17.0 4 hours – 35.7 8 hours – 66.3 12 hours – 89.4

TABLE 3. API CHARACTERIZATION.

Description	**White to off white crystalline powder**
Bulk Density (g/mL)	0.54
Tapped Density (g/mL)	0.69
Compressibility Index (%)	22
Hausner Ratio	1.28
LOD (%) (105°C – Auto mode)	0.6
Particle Size Analysis By Malvern Mastersizer	D10 – 13.02 D50 – 61.37 D90 – 144.39

TABLE 4. DRUG EXCIPIENT COMPATIBILITY STUDY.

API + Excipients	**Tests**	**Initial**	**Duration / Storage Conditions**	
			2nd Week 60 °C	**4th Week 40°C/75%RH**
Clarithromycin	ASSAY, %	97.37	95.66	99.63
	TI %	1.124	1.148	1.110
	Moisture, %	1.17	1.09	1.21
Clarithromycin API + Microcrystalline cellulose (1:1)	ASSAY, %	98.49	96.02	107.45
	TI %	1.251	1.057	1.025
	Moisture, %	1.42	1.73	1.05
Clarithromycin API + Lactose Monohydrate (1:1)	ASSAY, %	101.74	97.12	97.97
	TI %	1.370	1.083	1.446
	Moisture, %	1.63	1.51	1.73
Clarithromycin API + Hypromellose 100,000 cps (1:1)	ASSAY, %	100.13	97.88	102.85
	TI %	1.348	1.167	1.303
	Moisture, %	1.35	2.36	2.14
Clarithromycin API + Sodium Alginate High Viscosity (1:1)	ASSAY, %	96.20	96.46	97.76
	TI %	0.964	1.234	1.228
	Moisture, %	1.68	3.08	3.33
Clarithromycin API + Ethyl Cellulose (1:1)	ASSAY, %	96.30	95.32	97.15
	TI %	1.067	1.054	1.088
	Moisture, %	1.61	1.21	1.41
Clarithromycin API + Colloidal Silicon Dioxide (1:0.1)	ASSAY, %	95.06	95.65	95.17
	TI %	1.059	1.035	1.179
	Moisture, %	1.30	1.30	1.32
Clarithromycin API + Stearic acid (1:0.1)	ASSAY, %	95.37	95.41	100.13
	TI %	1.182	1.058	1.093
	Moisture, %	1.40	1.33	1.42

Clarithromycin API + Talc (1:0.1)	ASSAY, %	95.85	95.82	99.75
	TI %	1.136	1.204	1.129
	Moisture, %	1.33	1.22	1.31
Clarithromycin API + Glyceryl Behenate (1:0.1)	ASSAY, %	95.58	96.39	97.45
	TI %	1.028	1.242	1.102
	Moisture, %	1.16	1.38	1.50
Clarithromycin API + Magnesium Stearate (1:0.1)	ASSAY, %	94.84	94.33	96.29
	TI %	1.121	1.015	1.132
	Moisture, %	1.28	1.30	1.39

TI% - % Total Impurity; Moisture, % - Water by Kf.

TABLE 5. BLEND AND TABLET CHARACTERIZATION.

Particulars	**Batch No**				
	A	**B**	**C**	**D**	**E**
Dry Mix Bulk Density (g / ml)	0.35	0.50	0.41	0.37	0.38
Prelubrication Blending Time (min)	15	15	15	15	15
Lubrication Blending Time (min)	5	5	5	5	5
Bulk Density (g/ml)	0.44	0.54	0.41	0.45	0.45
Tapped Density (g/ml)	0.58	0.69	0.55	0.58	0.60
Compressibility Index (%)	24	22	26	22	25
Hausner Ratio	1.32	1.28	1.34	1.29	1.33
LOD of Final Blend (%)	2.79	2.13	2.70	2.56	2.78
Repose Angle (°)	30	31	30	31	31
Particle Size Analysis Data	% Blend Retained				
#20 ASTM	0.0	0.0	7.1	0.0	0.0
#40 ASTM	0.0	2.5	33.3	0.0	0.0
#60 ASTM	7.5	5.0	14.3	5.0	5.0
#80 ASTM	10.0	15.0	11.9	5.0	15.0
#100 ASTM	10.0	12.5	9.5	5.0	10.0
#140 ASTM	20.0	17.5	16.7	15.0	20.0
#200 ASTM	25.0	20.0	2.4	20.0	25.0
Pan	27.5	27.5	4.8	50.0	25.0
Average Weight (mg)	1145-1162	1151-1166	1169-1181	1171-1184	1173-1189
Average Thickness (mm)	8.32-8.36	8.31-8.35	8.12-8.19	8.16-8.22	8.15-8.21
Average Hardness (kP)	13-17	15-18	18-32	14-17	18-32
Friability (%)	0.04	0.06	0.04	0.04	0.05
Picking and Sticking	✓	✓	-	-	-
Dissolution Time in Hours	Mean % Drug Dissolved				
USP-II (Paddle), 2	19.3	25.4	11.6	19.0	17.3
50 RPM, 900 mL, 4	45.1	48.8	24.4	39.3	34.3
pH 6.0 Phosphate 8	89.3	79.5	49.5	72.4	64.0
Buffer 12	102.5	90.6	71.1	92.0	89.6

TABLE 6 MILLING OPTIMIZATION STUDY.

	Time in Hours	**% Drug Dissolved**			
Dissolution: USP-II (Paddle),	2	24.9	26.1	22.3	26.3
50 RPM, 900 mL, pH 6.0 Phosphate	4	51.8	53.1	44.2	45.8
Buffer.	8	82.4	92.3	82.1	77.6
	12	95.0	99.0	95.4	90.0
Milling Screen Used (mm)		0.5	0.7	0.8	1.0

TABLE 7 – OPTIMIZATION OF PRELUBRICATION BLENDING TIME.

Blend Uniformity (% Assay of API) in 10 Different Locations										
Blending Time	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
10 min	96.34	97.06	96.29	95.83	100.51	96.06	94.74	98.91	98.52	97.09
15 min	94.72	96.55	95.54	95.63	96.80	97.04	96.35	97.38	96.41	96.05
20 min	95.94	97.59	96.95	96.46	96.57	96.72	96.92	97.75	97.85	97.45

TABLE 8 – INFLUENCE OF MACHINE SPEED ON WEIGHT VARIATION.

Speed (RPM)	Low (10)	Target (25)	High (32)
Average, mg	1171	1171	1175
Minimum, mg	1164	1163	1163
Maximum, mg	1182	1183	1186

TABLE 8 – INFLUENCE OF MACHINE SPEED ON CONTENT UNIFORMITY.

Speed (RPM)	Low (10)	Target (25)	High (32)
Average, %	98.73	98.20	98.71
Minimum, %	97.72	96.70	97.47
Maximum, %	99.59	99.13	99.87
%RSD	0.60	0.76	0.80

TABLE 9 – HARDNESS STUDY.

Hardness	Low (18 kP)	Target (25 kP)	High (32 kP)
Average, kP	19.00	24.83	29.70
Minimum, kP	17.80	23.80	28.90
Maximum, kP	21.10	25.60	32.00

TABLE 9 – INFLUENCE OF HARDNESS STUDY ON THICKNESS VARIATION.

Thickness	Low (18 kP)	Target (25 kP)	High (32 kP)
Average, mm	8.44	8.16	8.00
Minimum, mm	8.40	8.12	7.81
Maximum, mm	8.49	8.24	8.04

TABLE 9 – INFLUENCE OF HARDNESS STUDY ON % FRIABILITY.

Friability	Low (18 kP)	Target (25 kP)	High (32 kP)
Friability, %	0.01	Nil	Nil

TABLE 9 – INFLUENCE OF HARDNESS STUDY ON DISSOLUTION.

Dissolution Parameters: USP-II (Paddle), 50 RPM, 900 mL, pH 6.0 (0.05M phosphate buffer)
Mean % Drug Dissolved (n = 6 Units)

Particulars	Time in Hours				Remarks
	2	4	8	12	
Batch E	10.7	26.0	55.4	80.0	18 kP Hardness
	11.6	24.4	49.5	79.3	25 kP Hardness
	12.8	24.8	47.5	77.2	32 kP Hardness

TABLE 10 DISSOLUTION PROFILE COMPARISON OF TEST VS REFERENCE PRODUCT.

Dissolution Parameters: USP-II (Paddle), 50 RPM, 900 mL, pH 6.0 (0.05M phosphate buffer)
Mean % Drug Dissolved

Particulars	Time in Hours				Remarks
	2	4	8	12	
BIAXIN XL FILM TAB®	17.0	35.7	66.3	89.4	Marketed Product
Batch E	17.3	34.3	64.0	89.6	Test Product

TABLE 11 DISSOLUTION PROFILE COMPARISONS – MODEL INDEPENDENT APPROACH.

Particulars	Difference Factor (f1) *Should be 0-15*	Similarity Factor (f2) *Should be 50-100*
Batch E **Vs** BIAXIN® XL FILMTAB®	2	90

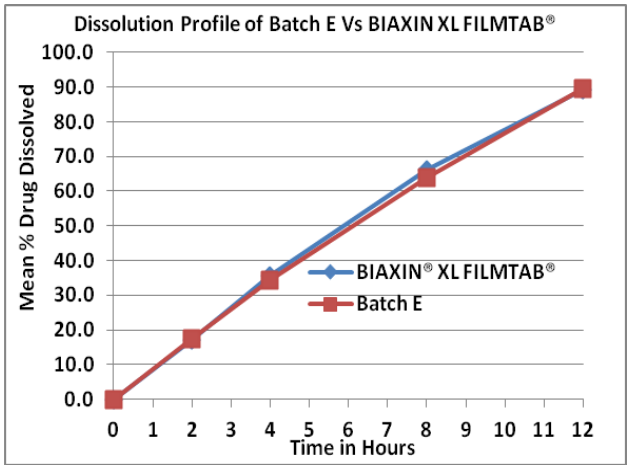

FIGURE 1 DISSOLUTION PROFILE COMPARISON OF BATCH E VS BIAXIN XL FILM TAB®

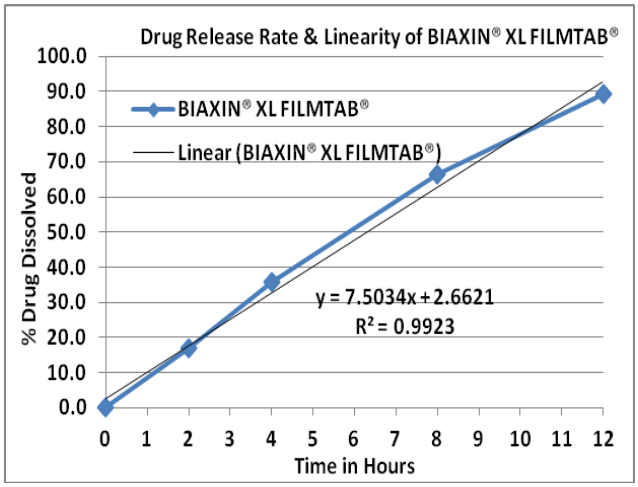

FIGURE 2 DRUG RELEASE RATE & LINEARITY OF BIAXIN XL FILMTAB®

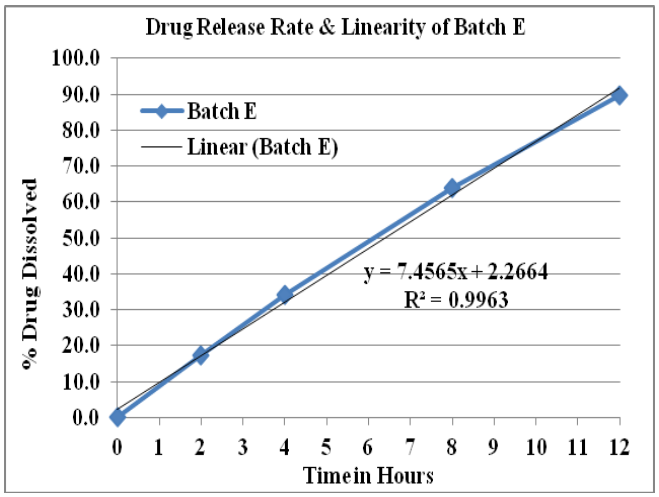

FIGURE 3 DRUG RELEASE RATE & LINEARITY OF BATCH E

TABLE 12 MATHEMATICAL MODELLING & KINETICS OF DRUG RELEASE.

Particulars	Correlation Coefficient (R^2)			
	Zero Order	First Order	Higuchi	Koresmeyer-Peppas
BIAXIN XL FILMTAB®	0.9923	0.6936	0.9388	0.8592
Batch E	0.9963	0.6959	0.9346	0.8579

TABLE 13 STABILITY RESULTS OF BATCH E AT 40°C ± 2°C / 75 ± 5% RH.

Test	Specification	Initial	1st Month	2nd Month	3rd Month
Description	*	**	**	**	**
Loss On Drying (%)	NMT 6.0	1.5	2.4	2.4	2.0
Assay (%)	90-110	96.7	96.7	96.3	96.9
Related Substances (%)					
Highest Unknown Impurity	NMT 0.2	0.076	0.080	0.085	0.091
Total Impurities	NMT 2.0	0.758	1.101	0.880	1.006
Dissolution	USP-II (Paddle), 50 RPM, 900 mL, pH 6.0 (0.05M phosphate buffer)				
Time (Hours)	Mean % Drug Release				
2	NMT 25	17.3	19.0	19.0	18.0
4	20%-40%	34.3	39.0	40.0	35.0
8	40%-75%	64.0	72.0	73.0	61.0
12	NLT 75%	89.6	95.0	92.0	83.0

*White to off white, film-coated, oval-shaped extended-release tablets. **Complies.

TABLE 14 STATISTICAL ANALYSIS OF PHARMACOKINETIC DATA – FASTED STUDY.

Product / Statistics	C_{max} (ng / mL)	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	T_{max} (h)
Test Product				
Arithmetic Mean	1129.5667	17069.4633	17527.8706	
Geometric LS Mean	1068.3793	15346.0240	15749.5200	8.0079
Standard Deviation	357.238	6549.7696	6809.5651	
Reference Product				
Arithmetic Mean	1160.6035	18788.3285	19274.3612	
Geometric LS Mean	1084.4029	16591.5680	17031.8990	9.3810
Standard Deviation	392.9202	7910.6582	8147.4666	
T/R (%)	98.52	92.49	92.47	
90% Confidence Interval (T/R)				
Lower Limit (%)	92.25	84.61	84.77	
Upper Limit (%)	105.22	101.10	100.87	
ISCV (%)	22.34	30.56	29.81	

TABLE 15 STATISTICAL ANALYSIS OF PHARMACOKINETIC DATA – FED STUDY.

Product / Statistics	C_{max} (ng / mL)	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	T_{max} (h)
Test Product				
Arithmetic Mean	1805.5470	19090.9356	19449.5591	
Geometric LS Mean	1592.8541	17324.015	17709.215	5.4206
Standard Deviation	756.7170	8301.7410	8411.4252	
Reference Product				
Arithmetic Mean	1724.1793	19260.4181	19650.1481	
Geometric LS Mean	1582.0234	18046.367	18431.773	4.6746
Standard Deviation	623.7752	7215.9313	7342.9506	
T/R (%)	100.68	96.00	96.08	
90% Confidence Interval (T/R)				
Lower Limit (%)	91.82	88.65	88.93	
Upper Limit (%)	110.4	103.95	103.81	
ISCV (%)	31.71	27.22		

STABILITY STUDY

Finalized extended release tablets of Clarithromycin were subjected to accelerated stability study and there was no change in the different physico-chemical parameters of the tablets. See Table 13 for further details.

IN-VIVO STUDY

In vivo studies were carried out for test formulation and reference product. The plasma levels of Clarithromycin were determined. The mean concentration-time profiles for the marketed and test product of Clarithromycin under fasted and fed condition were shown in Table 14 & Table 15 respectively. T/R ratio of 12 volunteers shows that the test product is bioequivalent to the marketed formulation.

CONCLUSION

Extended-Release matrix tablets of Clarithromycin, 500 mg were formulated by wet granulation process using FBP. The composition utilized a combination of 210 mg of Hypromellose 15 cps and 440 mg of Hypromellose 5 cps as polymers to tailor the drug release. The manufacturing process was completely optimized with respect to granulation, milling, blending and compression. The prepared ER tablets of Clarithromycin were film coated upto 3% w/w build up using Opadry II White 85F18422. The physico-chemical properties of the finalized ER tablets of Clarithromycin was found to be stable at accelerated temperature and humidity conditions of 40°C / 75% RH for 3 months. The dissolution profile of the prepared extended-release tablets of Clarithromycin showed comparable in vitro dissolution and in vivo bio equivalence under fast and fed condition with that of marketed product BIAXIN XL FILM TAB®. Linearity by Correlation coefficient, drug release rate, similarity and difference factor determination by model independent approach and mathematical model of drug release kinetics were determined using dissolution profiles of both test and marketed product and were comparable. Both test and marketed product shows drug release profile following zero order kinetics.

COMPETING INTERESTS

The authors declare no conflict of interest.

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