Original Article

PHARMACOKINETIC STUDY OF OLOPATADINE 10 MG EXTENDED RELEASE TABLET IN COMPARISON WITH OLOPATADINE 5 MG IMMEDIATE RELEASE TABLET IN INDIAN POPULATION

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ABSTRACT

Objective: This study was designed to assess the pharmacokinetics of single dose of olopatadine hydrochloride 10 mg extended release (ER) tablet of Ranbaxy laboratories limited (two test formulations) with two doses of Allelock® 5 mg immediate release (IR) tablets of Kyowa Hakko Kogyo Co. Ltd. (reference formulation R), in healthy, adult, Indian male subjects under fed condition.

Methods: Fifteen healthy male volunteers, 26.07±6.62 y in age and 57.17±6.68 kg in body weight, were divided into three groups and received either olopatadine hydrochloride 10 mg ER tablet or two doses of Allelock® 5 mg tablets in each period. Blood samples were taken at predetermined time points and plasma concentrations of olopatadine were monitored by liquid chromatography mass spectrometric (LCMS/MS). Pharmacokinetic (PK) parameters AUC0-t, AUC0-24, AUC0-∞, and Cmax were calculated for olopatadine using WinNonlin. A statistical analysis was performed on PK data using SAS system.

Results: The ER formulations showed a similar AUC as compared to the IR formulation and there was no statistically significant difference in AUC of test formulation A and B and reference R. The ratios of AUC0-t, AUC0-24 and AUC0-∞ for A/R were 91.08, 94.90 and 91.32 and for B/R were 89.63, 93.95 and 89.63 respectively. The ER formulations reported a higher Cmax value as compared to IR formulation. The ratios of Cmax for A/R and B/R were 151.09 and 167.96 respectively. But these higher Cmax values did not pose any safety issue as there were no serious adverse events reported during the study.

Conclusion: In conclusion, we can say that though the study drugs did not meet the bioequivalence criteria set by regulatory agencies, but this study gave an insight about PK properties of olopatadine extended release formulation and given an idea about effect of smoking on the PK profile of olopatadine which can be studied in future.

Keywords: Olopatadine, Antihistaminic, Antiallergic, Pharmacokinetic, Bioavailability, Extended-release, Smoking

INTRODUCTION

Extended release (ER) or modified release (MR) mode of drug administration has certain advantageous impact on the magnitude of the pharmacologic response: (a) it minimizes fluctuation in blood drug concentrations', (b) it produces a slow input rate which tends to minimize the body's counteraction to the drug's intervening effect on regulated physiological processes; and (c) it provides a continuous mode of drug administration [1]. ER or MR formulations provide higher maximum plasma concentrations with lower inter-patient variability than the conventional, immediate release (IR), twice-daily formulations. Additionally, therapeutic drug levels with ER formulations achieved rapidly and maintained over the course of 24 h, allowing once-daily dosing. The studies have also confirmed good tolerability and safety of ER formulations similar to the IR formulations [2]. Another undoubted advantage of ER formulation is improved patient compliance. Compliance improves dramatically as prescribed dose frequency decreases [3-6]. The therapeutic effectiveness of a drug depends upon its bioavailability to elicit the desired pharmacological response. There are many drug-related (physicochemical properties) and host factors (physiological factors like age, blood flow to gastrointestinal tract (GIT), pH, gastric emptying etc.) that influence the rate and absorption of the drugs [7].

Allergic rhinoconjunctivitis and chronic urticaria, as well as eczema and bronchial asthma, are associated with a hypersensitive response of the immune system. This occurs following the interaction of allergen with a specific antibody that has been adsorbed onto the surface of mast cells and basophils located in the tissue and blood, respectively. Allergic rhinitis and conjunctivitis, which are the most common forms of atopic disease, are characterized by sneezing, rhinorrhoea, nasal obstruction and itching of the nose and eyes. There are many antiallergic and antihistaminic drugs for the treatment of rhinoconjunctivitis, urticaria, eczema and bronchial asthma. However, the incidence of these allergic diseases in general has been increasing. As the prevalence of these allergic diseases rises, efforts at the discovery of novel and effective medications for prevention and treatment of these conditions also rise [8].

Olopatadine hydrochloride is a novel antiallergic/histamine H1-receptor antagonist. It is a potent histamine H1-receptor antagonist and a specific mast cell stabilizer, with additional anti-inflammatory properties. Olopatadine hydrochloride principally acts as a selective histamine H1 receptor antagonist. Olopatadine is indicated for allergic rhinitis, urticaria, itching resulting from skin diseases (eczema/dermatitis, prurigo, pruritus cutaneous, psoriasis vulgaris, multiform exudative erythema) [9].

Olopatadine is approved as an ophthalmic solution in Europe, Japan, and the United States. In Japan, the molecule is also available as an oral formulation (Allelock®; Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan) for treatment of allergic conditions9. Allelock® conventional tablets are currently administered twice daily, in the morning and before going to bed. Hence, it is advantageous to formulate once daily dosage regimen for olopatadine hydrochloride as it will exhibit better patient compliance in outpatient therapy. Therefore, the present study was designed to evaluate bioavailability of single dose of olopatadine hydrochloride 10 mg extended release tablet (two formulations) of Ranbaxy laboratories limited in comparison with two doses of Allelock® 5 mg tablets of Kyowa Hakko Kogyo Co. Ltd., in healthy, adult, human male subjects under fed condition. This is the first study of olopatadine hydrochloride 10 mg extended release tablet in Indian population.

MATERIALS AND METHODS

Study design

The study was carried out in accordance with the basic principles defined in US 21CFR Part 320, USFDA guidance for industry for conducting bioavailability and bioequivalence Studies for orally administered drug products--general consideration 2003, ICH (62 FR25692, 09 May 1997)' Guidance for 'Good Clinical Practice', ICMR 'ethical guidelines for biomedical research on human participants (2006)', CDSCO 'guidance for Good Clinical Practices for Clinical Research in India' and the principles enunciated in the Declaration of Helsinki [10-14]. The study protocol was approved by the Jamia Hamdard Institutional Review Board. Adequate numbers of subjects were selected randomly from the volunteer bank of the clinical pharmacology unit (CPU) and all the subjects underwent a standardized screening procedure. All subjects were informed with objectives, treatments, potential risks, dates and activities during the clinical part of study. A written consent form was signed by each enrolled subject.

The study was designed as an open label, balanced, randomized, three-treatment, three-period, three-sequence, crossover comparative bioavailability study in healthy, adult, human male subjects under fed condition. During all the three periods of the study, subjects reported to CPU at least 12 h before dose administration on day 1. After sampling for 36 h post dose as per schedule, subjects were discharged on the evening of day 2. Post-admission to CPU during all the three periods of the study, all subjects were fasted overnight for at least 10 h before the high-fat high-calorie breakfast. There was 6 d washout period between the administrations of study drugs in each period.

Study drugs

The test product were two formulations of olopatadine hydrochloride 10 mg extended release tablet manufactured by Ranbaxy Laboratories Limited, India (batch number RV (4430)01, RV (4430)05, expiry date February 2012) and the reference product was Allelock® 5 mg tablet manufactured and distributed by Kyowa Hakko Kogyo Co. Ltd., Japan (batch number 109AIH, expiry date August 2012). Morning dose was administered with 240 ml of drinking water at ambient temperature, 45 min after starting of high fat high calorie breakfast in all the three periods of the study. In case of reference product, evening dose was administered with 240 ml of drinking water at ambient temperature, 45 min after starting of high fat high calorie dinner in all the three periods of the study. The order of receiving study treatments for each subject during the three periods of the study was determined according to the SAS-generated balanced randomization schedule.

Study subjects

Subjects who have voluntarily given written informed consent to participate in this study were selected based on inclusion/exclusion criteria like age range of 18-45 y, neither overweight nor underweight for his height and have haemoglobin ≥ 13.0 g/dl etc. Medical history and demographic data, including name, sex, age, body weight (kg), height (cm) and tobacco use (including number of cigarettes smoked per day) were recorded. Each subject underwent physical examination and the laboratory tests of hematologic, hepatic/renal functions, urinalysis, serology and ECG. Fifteen medically healthy subjects with clinically normal laboratory profiles were selected based on the inclusion/exclusion criteria as per protocol. The subjects did not take any prescription, OTC medications and vitamins for at least 30 d prior to the start of study and during the study. All the subjects consumed the meal as per the meal schedule and abstained from any alcohol/products containing alcohol and grapefruit juice and/or grapefruit supplements for 48 h prior to admission and till last sample collection for pharmacokinetic analysis in all the three periods of the study. Subjects also abstained from tea, coffee, cigarette and any other xanthine containing beverages, during in-house stay in all the three periods of the study.

During the study periods, all the subjects were under medical supervision. Vital signs were examined at scheduled time as per the protocol.

Blood sampling

Blood samples from each subject were collected in prechilled K3 ethylenediamine tetraacetic acid (EDTA) vacutainers through indwelling heparinized cannula placed in forearm veins.

The blood samples were collected pre-dose (in duplicate) and at 0.250, 0.500, 0.750, 1.000, 1.500, 2.000, 2.500, 3.000, 3.500, 4.000, 5.000, 6.000, 7.000, 8.000, 10.000, 12.000, 16.000, 24.000, 30.000 and 36.000 h post-dose from subject of test-arm and at 0.167, 0.250, 0.333, 0.500, 0.667, 0.833, 1.000, 1.333, 1.667, 2.000, 2.500, 3.000, 4.000, 6.000, 8.000, 10.000, 12.000, 12.167, 12.250, 12.333, 12.500, 12.667, 12.833, 13.000, 13.333, 13.667, 14.000, 14.500, 15.000, 16.000, 18.000, 20.000, 24.000, 30.000 and 36.000 h post morning dose from subjects of reference-arm in all the three periods of the study.

The pre-dose blood samples in all the three periods of the study were collected within a period of approximately 1.5 h before the morning dose and the post-dose samples were generally collected within 2 min of the scheduled time. After collection, the blood samples were centrifuged at a speed of 4000 RPM for duration of 15 min and at a temperature of 4±2 °C under refrigeration as soon as possible to separate plasma. All post dose plasma samples were divided into two aliquots and transferred to suitably labelled tubes. The plasma samples were then stored at below-50 °C, pending transfer to the analytical facility for assay.

Sample analysis

A liquid chromatography mass spectroscopy (LC-MS/MS) method for the estimation of olopatadine in human plasma was developed and validated by using Olopatadine-d3 as internal standard (ISTD). The validation of this procedure was performed to evaluate the method in terms of selectivity, linearity, precision, accuracy, sensitivity, recovery and stability [15]. The procedure involved solid phase extraction with oasis HLB 1CC cartridges. The drug and the ISTD were eluted from a Zorbax eclipse XDB C18, 100x4.6 mm, 3.5µM column at 30 °C with a mobile phase consisting of 0.02% formic acid solution: methanol (40:60) (v/v) at a flow rate of 1 ml/min. Mass spectrometric detector was used to measure the drug and ISTD using multiple reaction monitoring. Each analysis requires no longer than 2.5 min. Quantification was achieved by measurement of the peak area ratio of the drug to the ISTD. The limit of the quantification of olopatadine in human plasma was 1.0023 ng/ml.

Pharmacokinetic analysis

The concentration data obtained from analytical study was entered in WinNonlin pharmacokinetic software for further processing. The PK parameters were calculated for olopatadine using WinNonlin Node version 5.0.1 from Pharsight. Area under the curve (AUC) values like AUC_{0-t} (AUC from time zero to the last measurable concentration), AUC_{0-24} (AUC from time zero to 24 h) were calculated by the linear trapezoidal method. $AUC_{0-\infty}$ (AUC from time zero to infinity) is calculated as the sum of AUC_{0-t} plus the ratio of the last measurable plasma concentration to the elimination rate constant. $AUC_{\%Extrap}$ (the percentage of extrapolated AUC from the last measurable concentration to infinity) was calculated as $[(AUC_{0-\infty}-AUC_{0-t})/AUC_{0-\infty}]* 100$. The maximum plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were taken directly from observed concentration vs time data. K_{el} (elimination rate constant) was calculated from a semi-log plot of the plasma concentration versus time curve. The parameter was calculated by linear least-square regression analysis using the maximum number of points in the terminal log-linear phase (e. g. three or more non-zero plasma concentrations). $T_{1/2}$ (elimination half-life) was calculated as $0.693/K_{el}$.

Statistical analysis

Statistical analysis was performed using the WinNonlin PK Software, Version 5.0.1. The analysis included the data from all subjects who have completed the study. Arithmetic means, standard deviations and coefficients of variation were calculated for the abovementioned PK parameters. Additionally, geometric means and percentage coefficient

of variation of geometric means was calculated for AUC_{0-t}, AUC_{0-24}, $AUC_{0-\infty}$ and C_{max}. The log-transformed PK parameters (C_{max}, AUC_{0-t}, AUC_{0-24}, $AUC_{0-\infty}$) for Test (A and B) and Reference (R) formulations were analysed using a mixed effects ANOVA (Analysis of variance) model. Each analysis of variance included calculation of least-squares means (LSM), the difference between the adjusted formulation means and the standard error associated with the difference. The above analyses were done using the appropriate SAS® procedure. The ratio of the test (A or B) and reference (R) product averages (least square means) was calculated for olopatadine by first calculating the differences in the averages (arithmetic means) of the log-transformed data and then taking the antilog of the obtained difference. The comparison of interest was A vs R and B vs R, so the ratios was of the form A/R and B/R. Ratio of means was expressed as a percentage of the LSM for the reference formulations.

RESULTS

Fifteen [15] healthy, adult, human male subjects, who met the inclusion and exclusion criteria as described in the protocol, were enrolled in the study. Thirteen [16] subjects completed all the three periods of the study as two subjects were withdrawn from the study (one was withdrawn due to adverse event and another subject failed to comply with requirement of protocol). The mean age of the subjects was 26.07±6.62 y (ranged from 18-38 y) and mean weight was 57.17±6.68 Kg (ranged from 46.9-69.5 kg). The mean height of the subjects was 167.39±7.63 cm (ranged from 156–185 cm).

Demographic data of the subjects are provided in table 1. Data from all the subjects who completed the study were included in the final PK analysis. Vital signs of oral temperature, sitting blood pressure and radial pulse were found to be normal for all the subjects during the course of the study in all the three periods of the study. The clinical examination of all subjects was found to be normal. The study treatments were well tolerated by the study subjects, except one subject who experienced vomiting and epigastric pain and subsequently withdrawn from the study.

Two peaks were observed in the mean plasma concentration and time curve of IR formulation R, this was due to the 12-hourly administration of the formulation. Graphs are presented in fig. 1 and 2. Pharmacokinetic data obtained in the study showed that that C_{max} attained by ER test formulations A and B was higher than the C_{max} of IR reference formulation R. There was statistically significant difference (p<0.0001) between the C_{max} of test formulations A and B and reference formulations R. In relation to area under the curve, the results demonstrated that the ER formulations showed a similar extent of abortion as compared to the reference formulation and there was no statistically significant difference (p<0.0001) in AUC of test formulations A and B and reference R. All the values for 90% confidence intervals for log transformed data of C_{max}, AUC_{0-36}, AUC_{0-24} and $AUC_{0-\infty}$ were within the stated regulatory bioequivalence range of 80-125% [17, 19] except for C_{max}, therefore, bioequivalence between test products A, B and reference product R cannot be established. Detailed data are presented in tables 2, 3 and 4.

Table 1: Demographic details of subjects

| Demographic details of subjects								
Subject No.	Age (year)	Weight (kg)	Height (cm)	BMI (kg/m²)	Diet	Gender	Smoking	Race
1	21	50.8	169.4	17.70	NV	Male	Yes	Asian
2	26	58.8	168.8	20.64	NV	Male	No	Asian
3	31	59.9	172.1	20.22	NV	Male	No	Asian
4	25	69.5	185	20.31	NV	Male	No	Asian
5	18	50.5	163.3	18.94	NV	Male	No	Asian
6	30	57	162.3	21.64	NV	Male	No	Asian
7	38	60.8	159.7	23.84	NV	Male	No	Asian
8	35	65.5	168.8	22.99	NV	Male	No	Asian
9	20	64	181.4	19.45	V	Male	No	Asian
10	21	61.8	162.7	23.35	NV	Male	No	Asian
11	19	57.9	167	20.76	NV	Male	Yes	Asian
12	21	54.9	156	22.56	NV	Male	No	Asian
13	30	50.2	165.5	18.33	NV	Male	No	Asian
14	21	49	162.9	18.47	NV	Male	No	Asian
15	35	46.9	166	17.02	NV	Male	No	Asian
Mean	26.07	57.17	167.39					
±SD	6.62	6.68	7.63	BMI = Body Mass Index				
% CV	25.38	11.68	4.56	NV= Non-vegetarian; V= Vegetarian				
N	15	15	15					
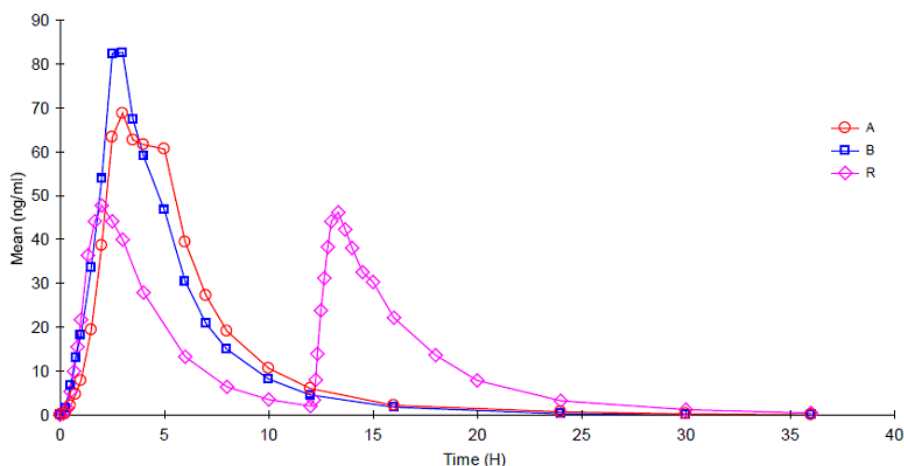
Fig. 1: Linear plot of mean plasma olopatadine concentration (ng/ml) versus time (h)
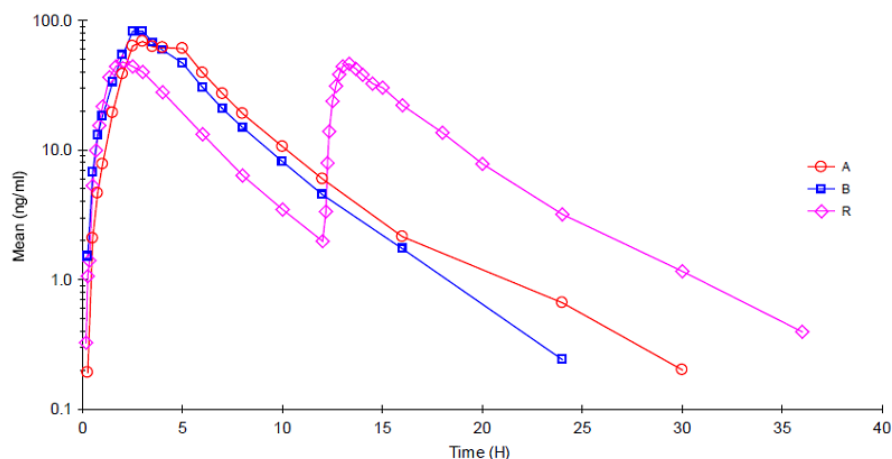
Fig. 2: Semilog plot of mean plasma olopatadine concentration (ng/ml) versus time (h)

Table 2: Pharmacokinetic results (N=14)

Product	C_{max} (ng/ml)*	T_{max} (h)*	AUC_{0-24} (ng. h/ml)*	AUC_{0-36} (ng. h/ml)*
A	100.33 (±29.60)	3.73 (±1.13)	387.60 (±59.02)	385.56 (±62.25)
B	112.38 (±37.05)	3.00 (±1.00)	377.60 (±74.75)	372.81 (±75.90)
R	65.18 (±17.86)	8.41 (±5.78)	403.64 (±93.26)	418.27 (±100.51)

*Mean values are presented

Table 3: Summary statistics of different PK parameters (N=14)

Parameters	Product A	Product B	Product R
Mean C_{max} (ng/ml)*	95.6178	106.6336	62.9773
Mean AUC_{0-36} (ng. h/ml)*	380.80621	365.64849	407.55943
Mean AUC_{0-24} (ng. h/ml)*	383.36735	370.84072	394.36214
Mean $AUC_{0-\infty}$ (ng. h/ml)*	388.34376	372.16152	414.87231

*Log-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported

Table 4: 90% confidence intervals for log transformed data of test v/s reference

Formulations	Parameters			
	C_{max}	AUC_{0-36}	AUC_{0-24}	$AUC_{0-\infty}$
A v/s R	127.41-179.17	86.37-96.05	90.13-99.93	86.75-96.12
B v/s R	142.25-198.30	85.11-94.39	89.34-98.79	85.26-94.22

DISCUSSION

Olopatadine is available in its conventional IR form to be administered twice a day. An undoubted advantage of ER formulations over conventional dosage forms is improved patient compliance; compliance improves dramatically as prescribed dose frequency decreases [3-6]. Apart from improved patient compliance, there is decreased fluctuation in steady state levels leading to better control of disease condition and reduced intensity of local and systemic side effects [5, 16, 17].

In this study, higher C_{max} values of test formulations A and B were reported as compared to reference formulation R, there was statistically significant difference in C_{max} between reference formulation and test formulation A and B as A/R and B/R ratio values were 151.09 and 167.96 respectively which were higher than the defined regulatory range of 80% to 125%. In a comparative bioavailability study conducted to examine the pharmacokinetics of prochlorperazine immediate release tablet and sustained release tablet in healthy, adult, male volunteers, the reported C_{max} values for sustained release tablet and immediate release tablet were 297.89 and 218.41 ng/ml respectively [18], the similar pattern is shown in our study where the Cmax values of the sustained release formulations were higher than the immediate release.

The reason for higher Cmax of test formulations A and B than the reference formulation was possibly due to the fact that in first 2-3 h these formulations behaved similar to IR formulation. Another possible reason of the higher Cmax values of extended release test formulations could be dose dumping. Dose dumping is defined as unintended, rapid drug release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified release dosage from. Dose dumping can pose a significant risk to patients, either due to safety issue or diminished efficacy or both. Generally, dose dumping is observed due to a compromise of the release-rate-controlling mechanism [19]. It is often reported when a modified oral dosage from is conjunction with high fat food or alcohol. Hendeles *et al.* reported dose dumping phenomenon in a study conducted on theophylline extended release tablets taken under fed conditions. They reported that food caused precipitous doe-dumping resulting in dose normalized peak levels in in the serum that averaged 2.3 times higher than after a fasting dose [20]. Another study of nifedipine ER tablets in healthy volunteers reported an increase in plasma concentration of the test drug after a high fat breakfast. The test product developed a dose-dumping effect after the intake of food. This phenomenon went along with a loss in modified release characteristics [21].

In our study, extended release formulations showed a similar pattern which indicates a possible dose dumping effect. Major

portion of olopatadine from both the extended release test formulations was released in first few hours leading to a failure in the modified release characteristics of the formulation. However, these higher Cmax values of extended release formulations cannot be confidently attributed to the dose dumping phenomenon, as to confirm this we need to perform a similarly designed study in fasted state with a similar set of subjects. Another noteworthy observation in the study was that the maximum Cmax values for both the test formulations were reported from the same subject who is a regular smoker, so it is possible that regular smoking may have produced some changes in the normal physiological processes of the subject which ultimately caused the higher release of the of the drug from the ER formulations. Numerous drug interactions have been identified with tobacco smoke [22] and many regulatory agencies like Canadian, European and WHO recommend that preferably a non-smoker should be included in the bioequivalence studies [23-25]. But this can only be confirmed when another study in planned with both smoker and non-smoker subjects to study the effect of smoking on the pharmacokinetic parameters of olopatadine.

Nonetheless, these higher Cmax values of test formulation didn't pose any safety issue, as only one subject in test arm reported post-dose gastrointestinal adverse events which were not serious in nature and subject recovered without sequelae.

CONCLUSION

Based on pharmacokinetic and clinical results, it can be summarized that extended release formulation A and B achieved similar AUC as compared to reference drug but in both the test formulations most of the drug got released in initial few hours resulting in higher Cmax values but there were no safety concerns. Although the extended release formulations have showed a similar extent of absorption, but the products need to be reformulated in such a manner that slow drug release can be achieved as shown by lower Cmax and longer Tmax. In conclusion, we can say that though the study drugs did not meet the bioequivalence criteria set by regulatory agencies, but this study gave an insight about PK properties of olopatadine extended release formulation and given an idea about effect of smoking on the PK profile of olopatadine which can be studied in future.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

All authors declare that they have no conflict of interest.

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