American Journal of Psychiatric Rehabilitation Expert Opinion Article

Advancing In Antihistamine Delivery Systems: A Preclinical Evaluation of Levocetrizine Dihydrochloride Oral Spray

Laxmikant Harsola[1*], Dr Ashutosh Shukla[2], Dr Pragnesh Patani[3]

[1*,2]Department of Clinical Research, IISHLS, Indus University, Ahmedabad, India
[3]Khyati college of Pharmacy, Palodia Ahmedabad, India

***Corresponding author:** Laxmikant Harsola
*Indus University, Ahmedabad, India, Tel: +919662533266; Email: laxmikant.21.rs@indusuni.ac.in, laxmikantharsola76@gmail.com

Received- 29/04/2025 Acceptance- 01/05/2025

Abstract

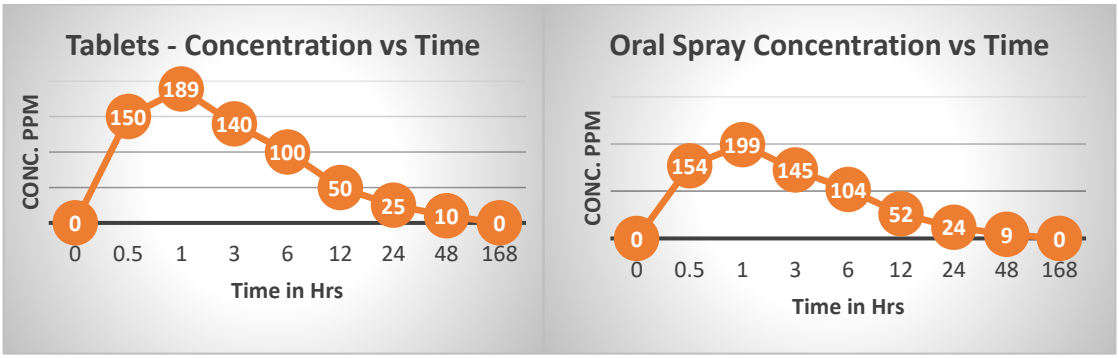
Objective: Levocetirizine dihydrochloride is also known as "Xyzol." Levocetirizine dihydrochloride is a second-generation piperazine derivative, potent H1 selective agent. Levocetirizine dihydrochloride is the active R (-) enantiomer of cetirizine dihydrochloride. In the case of an allergic or histaminic reaction, the medication must respond rapidly. Many older patients, infants, and dysphagia patients have trouble swallowing traditional tablets or capsules. Hence, a need exists for a relatively fast-acting oral spray form.

Methods: The oral spray were prepared by direct dissolving drug component into water with added buffering agents, sweetening agent, preservative and flavors. The oral spray was evaluated for general parameters like Appearance, Odor, pH and solution clarity. Then, the spray was filled in suitable plastic container having the spray device. Oral spray was evaluated for comparative pre clinical and bioequivalence against common tablet form.

Results: The oral spray Results demonstrated comparable systemic drug exposure for both formulations, with AUC values of 2731.25 ppm·hr and 2704.25 ppm·hr for the tablet and oral spray, respectively. The oral spray achieved a slightly higher Cmax (199 ppm) compared to the tablet (189 ppm), withboth formulations reaching Tmax at 1 hour. The elimination half-life was 15.83 hours for the tablet and 14.56 hours for the oral spray. Relative bioavailability of the oral spray was 99.01%, indicating bioequivalence within the accepted range.

Conclusion: Study concluded that oral spray system has several advantages like rapid drug availability in blood plasma allow drug for faster action. The rapid availability could enhance the onset of action, making it a favorable option for achieving faster therapeutic effects. The results show that Levocetirizine oral spray exhibited comparable pharmacokinetic parameters to the tablet formulation, including Cmax, Tmax, and elimination half-life. The faster absorption in the oral spray suggests it may provide quicker symptom relief in allergic reactions. Both formulations followed a similar elimination profile, with concentrations reaching near zero by 48 hours. This study supports the oral spray as a viable alternative to the tablet, particularly for patients with swallowing difficulties or those seeking more convenient administration. However, human studies are needed to confirm these findings and evaluate patient preferences.

Keywords: Levocetirizine dihydrochloride, Oral Spray, HPLC, Cmax, Tmax, Chromatography, Plasma, Bioequivalence, Concentration.



OBJECTIVE:

This study objective is to evaluate and compare preclinical data on Levocetirizine dihydrochloride oral spray with other available dosage forms, particularly oral tablets, to demonstrate advancements in antihistamine delivery.

BACKGROUND:

Various first-generation antihistamine drugs can be used in the treatment of allergy but not used because they cause sedation although initial second-generation drugs-like terfenadine and astemizole were found effective in allergic rhinitis and idiopathic urticaria without any sedation but had cardiac associated interactions. Other second-generation medications such as loratadine and cetirizine show efficacious in the treatment of allergic rhinitis and chronic idiopathic urticaria [1]. Levocetirizine dihydrochloride is a drug that comes under the category of second-generation antihistamine, and it an enantiomer levorotatory (-) form of cetirizine which is pharmacologically active and most selectively inhibit H1 histamine receptor [2]. Chemically levocetirizine dihydrochloride is (R)-[2-[4- [(4-chlorophenyl) phenylmethyl)-1-piperazinyl] ethoxy] acetic acid dihydrochloride. It is having the same pharmacological activity as cetirizine but produces less sedation as compared to cetirizine and thus more preferred nowadays [3]. Interestingly, levocetirizine has many other pharmacological consequences, partly linked to its H-1 antagonism. T lymphocytes, dendritic cells, and lung macrophages express the H-1 histamine receptor on their cell surface that induces activation molecules and cytokine and chemokine synthesis with proinflammatory effects when enabled [4]. It shows inhibitory action on keratinocytes, and also blocks the secretion of chemocytokine and granulocyte-macrophage colony-stimulating factor [5]. Adverse effects include fatigue, dry mouth, somnolence, pharyngitis, cough, and pyrexia. On overdose sigh and symptoms include drowsiness, agitation, and restlessness, so symptomatic treatment can be done, no antidote therapy is available for the overdose of levocetirizine dihydrochloride [6].

Oral spray forms small droplets that quickly adsorb to the mucosal surface and allow the drug to permeate into the blood circulation. The oral mucosa has shown encouraging results for the systemic absorption of many drugs due to the high permeability of the mucosal membrane. Oral sprays are very fast, the best effective and easy way to get daily dose for vitamins, minerals, and other nutrients ingredients. Due to this advantage oral sprays is seemed as an effective alternative of other oral medications as it bypassing the extensive first pass metabolism.

INTRODUCTION:

Levocetirizine Dihydrochloride is a commonly used antihistamine, typically administered as oral tablets for allergic conditions. This study explores the bioequivalence of a novel Levocetirizine oral spray, which may offer advantages like faster absorption and ease of administration. The study was conducted on rabbits, which provide a reliable model for pharmacokinetic studies due to their metabolic profile.

ABSTRACT:

This study assesses the bioequivalence of Levocetirizine Dihydrochloride (10 mg/mL) oral spray with its marketed tablet formulation by evaluating drug concentration in rabbit blood samples over time. The experiment was conducted under controlled conditions with specific age, weight, and ethical guidelines for animal subjects. Plasma drug concentrations were measured using high-performance liquid chromatography (HPLC). Results indicated comparable pharmacokinetic profiles for both formulations. The study highlights the oral spray as a potential alternative dosage form with similar therapeutic efficacy.

STUDY DESIGN:

This pilot bioequivalence study was conducted in compliance with ethical guidelines for animal testing. The study conducted by using of New Zealand white rabbits, divided into two groups, each group contained 5 rabbits.

- **Group B**: Rabbits received the Levocetirizine tablet.
- **Group C**: Rabbits received the Levocetirizine oral spray.

Animal Study Conditions:

- **Age**: 10-12 weeks
- **Weight**: 2.5-3.5 kg
- **Housing**: Rabbits were housed in individual cages under standard environmental conditions.
- **Diet**: Rabbits were fed a standard diet with free access to water. Fasting was done overnight before drug administration to ensure uniform absorption.

Drug Administration:

Group B received the tablet formulation, and Group C received the oral spray. Blood samples were collected at the following time points: pre-dose (0), 30 minutes, 1 hour, 3 hours, 6 hours, 12 hours, 24 hours, 48 hours, and 1 week (168 Hrs) post-administration.

Blood Sampling:

Approximately 1 mL of blood was collected from the marginal ear vein of each rabbit at each time point. The blood samples were immediately centrifuged at 3000 rpm for 10 minutes to separate plasma, which was stored at -20°C until analysis.

Analytical Conditions :

Instrument : HPLC (High Performance Liquid Chromatography)

Make : Shimadzu HPLC with UV detector

Column: C18 (5 µm, 250 × 4.6 mm)
Flow rate: 1 mL/min
Detection wavelength: 230 nm
Injection volume: 20 µL
PROCEDURE:

Plasma samples were prepared by adding 200 µL of plasma to 1 mL of acetonitrile for protein precipitation, followed by vortexing and centrifugation at 10,000 rpm for 10 minutes. The supernatant was filtered using a 0.22 µm membrane and injected into the HPLC system for analysis.

Pic -1 Albino Rabit

Pic -2 Sample collection from Albino Rabit ear vein

Pic -3 Albino Rabit after sample collection

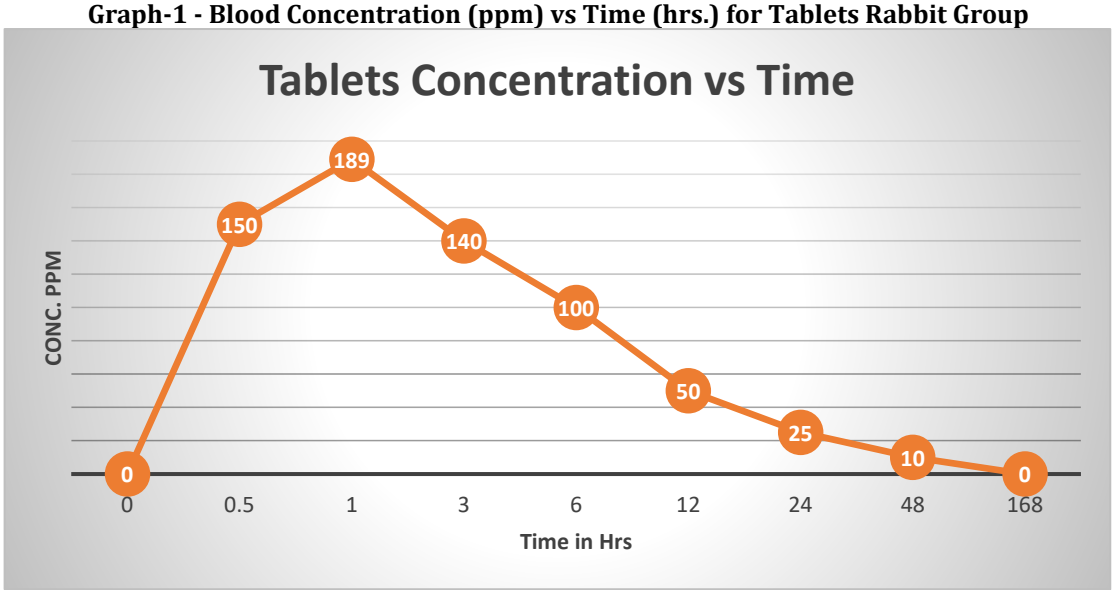
CALIBRATION AND QUALIFICATION:
A calibration curve was constructed by spiking blank plasma samples with known concentrations of Levocetirizine Dihydrochloride (ranging from 10 ppm to 200 ppm).The curve was used to quantify Levocetirizine concentrations in the rabbit plasma. The observed concentration vs time are as below -

Levocetrizine Tablet Group (Group B):

Table 1. Blood Concentration (ppm) vs Time (hrs.) for Tablets Rabbit Group

Time (Hr)	Concentration (PPM)
0	0
0.5	150
1	189
3	140
6	100
12	50
24	25
48	10
168	0

Graph-1 - Blood Concentration (ppm) vs Time (hrs.) for Tablets Rabbit Group



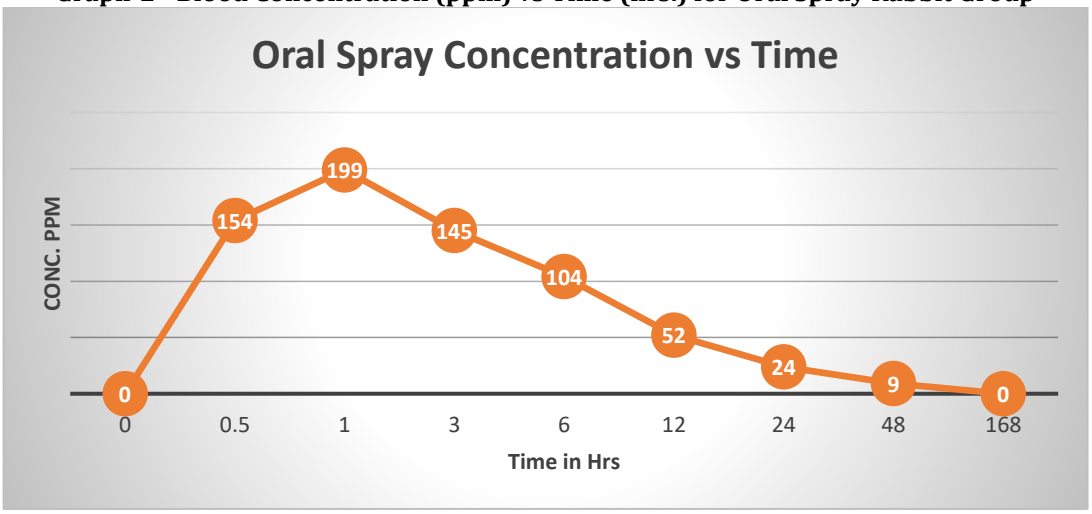
INFERENCE: Above tabulated data indicated the concentration peaked at 189 ppm at 1 hour, and declining gradually thereafter.

Levocetrizine Oral Spray Group (Group C):

Table 2. Blood Concentration (ppm) vs Time (hrs.) for Oral Spray Rabbit Group

Time (Hr)	Concentration (PPM)
0	0
0.5	154
1	199
3	145
6	104
12	52
24	24
48	9
168	0

Graph-2 - Blood Concentration (ppm) vs Time (hrs.) for Oral Spray Rabbit Group

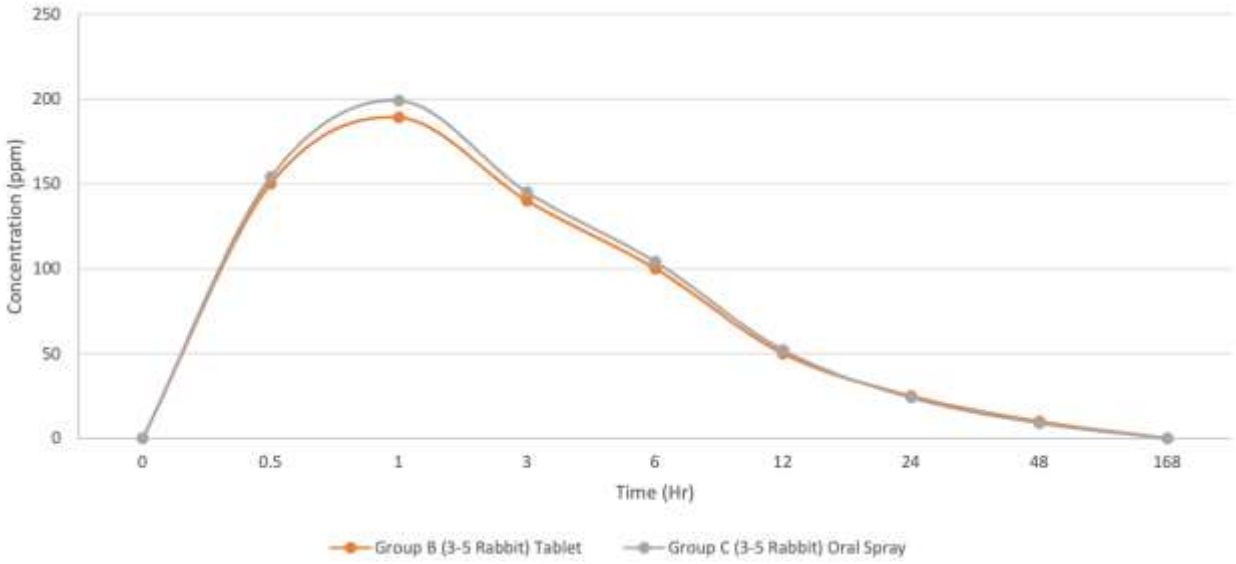


INFERENCE: Above tabulated data indicated the concentration peaked at 199 ppm at 1 hour, and declining gradually thereafter.

Table 3. Comparison of Oral Spray dosage form and Oral Sprey Plasma Concentration (ppm) vs Time (hrs.).

Sr. No.	Time	Group B (3-5 Rabbit) Tablet	Group C (3-5 Rabbit) Oral Spray
1	Predose	0	0
2	30 min	150 ppm	154 ppm
3	1 hr	189 ppm	199 ppm
4	3 hr	140 ppm	145 ppm
5	6 hr	100 ppm	104 ppm
6	12 hr	50 ppm	52 ppm
7	24 hr	25 ppm	24 ppm
8	48 hr	10 ppm	9 ppm
9	1 week	0	0 ppm

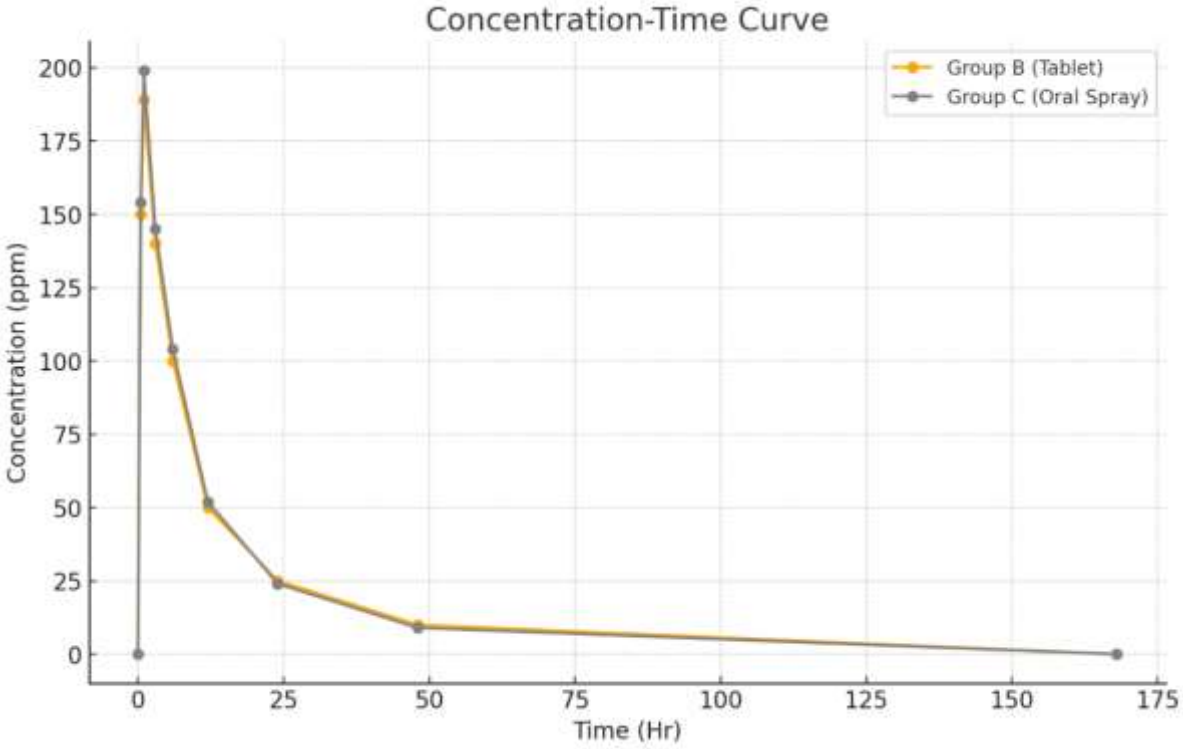
Graph 3. Comparison of Tablet dosage form and Oral Sprey Plasma Concentration (ppm) vs Time (hrs.).



INFERENCE:
• **Oral Tablet Group (B)**: The oral tablets reached the concentration peaked at 189 ppm at 1 hour, declining gradually thereafter.
• **Oral Spray Group (C)**: The oral spray reached a slightly higher peak of 199 ppm at
1 hour, with a similar elimination profile.

RESULTS FROM CONCENTRATION-TIME DATA CURVE:
Using Concentration vs time data to calculate:
1. **AUC (Area Under the Curve)** for both groups (tablet and oral spray).
2. **Cmax** (maximum concentration).
3. **Tmax** (time at which Cmax occurs).
4. **Half-life (t½)** using the elimination phase.
5. **Bioavailability** by comparing AUC values.
6. **Volume of distribution (Vd)**

Graph 4. Tablet dosage form and Oral Spray Plasma Concentration (ppm) -Time (hrs.) Curve



Parameter Group B (Tablet) Group C (Oral Spray)-
- **AUC** (Area Under Curve) 2731.25 ppm·hr 2704.25 ppm·hr
- **Cmax** (Maximum Concentration) 189 ppm 199 ppm
- **Tmax** (Time at Cmax) 1 hr 1 hr

OBSERVATIONS:
AUC: Both the tablet and oral spray formulations show nearly similar AUC values,
indicating comparable systemic drug exposure.
Cmax: The oral spray achieves a slightly higher maximum concentration (199 ppm)
compared to the tablet (189 ppm).
Tmax: Both formulations reach peak concentration at **1 hour**.

RESULTS:
Elimination Half-Life:
- Tablet Group: **15.83 hours**
- Oral Spray Group: **14.56 hours**

Bioavailability of Oral Spray (relative to Tablet): 99.01%
Area Under the Curve (AUC):
- Tablet Group (AUC): **2731.25**
- Oral Spray Group (AUC): **2704.25**

DISCUSSION:
This study evaluates the pharmacokinetics and bioequivalence of Levocetirizine Dihydrochloride in two formulations: an oral spray and a marketed tablet. The research was conducted using rabbit models under controlled experimental conditions. Blood samples were collected at predefined intervals, and plasma drug concentrations were analyzed using high-performance liquid

chromatography (HPLC). Pharmacokinetic parameters, including area under the curve (AUC), maximum plasma concentration (Cmax), time to reach Cmax (Tmax), elimination half-life (t½), and relative bioavailability, were calculated.

Results demonstrated comparable systemic drug exposure for both formulations, with AUC values of 2731.25 ppm·hr and 2704.25 ppm·hr for the tablet and oral spray, respectively. The oral spray achieved a slightly higher Cmax (199 ppm) compared to the tablet (189 ppm), with both formulations reaching Tmax at 1 hour. The elimination half-life was 15.83 hours for the tablet and 14.56 hours for the oral spray. Relative bioavailability of the oral spray was 99.01%, indicating bioequivalence within the accepted range.

These findings highlight the oral spray as a viable alternative to traditional tablets, offering potential benefits such as faster absorption and ease of administration. The study emphasizes the need for clinical trials in humans to confirm these results and explore the oral spray's utility in enhancing patient compliance and convenience.

INFERENCE:

From the above preclinical study data below is the summarized outcome as-

The results show that Levocetirizine oral spray exhibited comparable pharmacokinetic parameters to the tablet formulation, including Cmax, Tmax, and elimination half-life. The faster absorption in the oral spray suggests it may provide quicker symptom relief in allergic reactions. Both formulations followed a similar elimination profile, with concentrations reaching near zero by 48 hours.

This study supports the oral spray as a viable alternative to the tablet, particularly for patients with swallowing difficulties or those seeking more convenient administration. However, human studies are needed to confirm these findings and evaluate patient preferences.

CONCLUSION:

Study concluded that oral spray system has several advantages like rapid drug availability in blood plasma allow drug for faster action. The rapid availability could enhance the onset of action, making it a favorable option for achieving faster therapeutic effects.

ACKNOWLEDGEMENT:

The authors thankful with our deepest core of heart to Dr. Ashutosh Shukla and Prof. Dr Dharam Chand Jain, SAGE University INDORE, for his valuable guidance and all the others who directly and indirectly gave their support. Also thankful to Institutional Animal Ethics Committee (IAEC) of Khyati College of Pharmacy, and animal care followed the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Adequate measures were taken to minimize animal suffering.

CONFLICTS OF INTEREST:

Nil.

REFERENCE:

1. Dhiman S, Verma S. Optimization of melt-in-mouth tablets of levocetirizine dihydrochloride using response surface methodology. Int J Pharm Pharm Sci 2012;4:176-84.
2. Tripathi KD. Essentials of Medical Pharmacology. 8th ed. New Delhi: Jaypee Brothers Medical Publishers; 2018.
3. Beale JM, Block J. Wilson and Gisvold's Text Book of Organic Medicinal and Pharmaceutical Chemistry. New Delhi: Wolters Kluwer; 2011.
4. Triggiani M, Gentile M, Secondo A, Granata F, Oriente A, Taglialatela M, et al. Histamine induces exocytosis and IL-6 production from human lung macrophages through interaction with H receptors. J Immunol 2001;166:4083-91.
5. Giustizieri ML, Albanesi C, Fluhr J, Gisondi P, Norgauer J, Girolomoni G. H1 histamine receptor mediates inflammatory responses in human keratinocytes. J Allergy Clin Immunol 2004;114:1176-82.
6. Lachman L, Liberman HA, Kaing JL. The Theory and Practice of Industrial Pharmacy. 3rd ed. Bombay: Varghese Publishing House; 1987.
7. General Principles of Preclinical Study Design, Wenlong Huang, Nathalie Percie du Sert, Jan Vollert, and Andrew S. C. Rice *Published in final edited form as:* Handb Exp Pharmacol. 2020 Jan 1;257:55–69. doi: 10.1007/164_2019_277
8. Rice ASC (2010) Predicting analgesic efficacy from animal models of peripheral neuropathy and nerve injury: a critical view from the clinic. In: Mogil JS (ed) Pain 2010 – an updated review: refresher course syllabus. IASP Press, Seattle, pp 1–12
9. Rice AS, Cimino-Brown D, Eisenach JC, Kontinen VK, Lacroix-Fralish ML, Machin I, Preclinical Pain C, Mogil JS, Stohr T (2008) Animal models and the prediction of efficacy in clinical trials of analgesic drugs: a critical appraisal and call for uniform reporting standards. Pain 139:243–247. https://doi.org/10.1016/j.pain.2008.08.017
10. Baastrup C, Maersk-Moller CC, Nyengaard JR, Jensen TS, Finnerup NB (2010) Spinal-, brainstemand cerebrally mediated responses at- and below-level of a spinal cord contusion in rats: evaluation of pain-like behavior. Pain 151:670–679. https://doi.org/10.1016/j.pain.2010.08.024
11. E Nettis, G F Calogiuri, E Di Leo, F Cardinale, L Macchia, A Ferrannini & A Vacca (2009) Once

daily levocetirizine for the treatment of allergic rhinitis and chronic idiopathic urticaria, Journal of Asthma and Allergy, , 17-23, DOI: 10.2147/jaa.s3022

12. Jaipal, A., Pandey, M. M., Charde, S. Y., Sadhu, N., Srinivas, A., and Prasad, R. G. (2016). Controlled release effervescent buccal discs of buspirone hydrochloride: in vitro and in vivo evaluation studies. *Drug Deliv.* 23 (2), 452–458. doi: 10.3109/10717544.2014.917388
13. Kaur, G., Singh, D., and Brar, V. (2014). Bioadhesive okra polymer based buccal patches as platform for controlled drug delivery. *Int. J. Biol. Macromol.* 70, 408–419. doi: 10.1016/j.ijbiomac.2014.07.015
14. Khan, S., and Boateng, J. (2018). Effects of cyclodextrins (beta and gamma) and l-Arginine on stability and functional properties of mucoadhesive buccal films loaded with omeprazole for pediatric patients. *Polymers* 10 (2), 157. doi: 10.3390/polym10020157.
15. Shirsand SB, Shivanand, Shailashri, Keshavshetti G, Jonathan V. Hibiscus sabdariffa mucilage as a disintegrant in formulating fast dissolving tablets. J Pharm Sci 2016;15:143-9.
16. Kulkarni AR, Soppimath KS, Aminabhavi TM, Rudzinski WE. In vitro release kinetics of cefadroxil loaded sodium alginate interpenetrating network beads. Eur J Pharm Biopharm 2001;51:127-33.
17. Bagul U, Gujar K, Patel N, Aphale S, Dhat S. Formulation and evaluation of sublimed fast melt tablets of levocetirizine dihydrochloride. Int J Pharm Sci 2010;2:76-80.
18. Zhang H, Zhang J, Streisand JB (2002) Oral mucosal drug delivery clinical pharmacokinetics and therapeutic applications. ClinPharmacol 41: 661- 680.