IJPSR (2023), Volume 14, Issue 5 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 16 February 2023; received in revised form, 20 April 2023; accepted 22 April 2023; published 01 May 2023

FORMULATION AND EVALUATION OF pH TRIGGER NASAL *IN-SITU* GEL OF LEVOCETIRIZINE HYDROCHLORIDE FOR LOCALIZED TREATMENT OF ALLERGIC RHINITIS

Upasana Khatri [*1], Meenakshi Bharkatiya [2] and Sunil Saini [3]

Jai Narain Vyas University [1], Pharmacy Wing, Jodhpur - 342802, Rajasthan, India.
Bhupal Nobles' University [2], Udaipur - 313001, Rajasthan, India.
Raj Pharmacy College [3], Jodhpur-Jaipur Highway, Bawarla, Jodhpur - 342027, Rajasthan, India.

Keywords:

Allergic rhinitis, Antihistaminic, Levocetirizine hydrochloride, Nasal obstruction, Mucoadhesive strength, Viscosity, HPMC, Carbopol

Correspondence to Author:
Upasana Khatri

Assistant Professor,
Jai Narain Vyas University,
Pharmacy Wing, Jodhpur - 342802,
Rajasthan, India.

E-mail: iamupasana17@gmail.com

ABSTRACT: Objective: This dissertation work aimed to prepare Levocetirizine HCL (LCH) nasal in-situ gel, a second-generation antihistamine, to improve its retention time, sustain release, enhance the bioavailability, and avoid first-pass metabolism. **Process:** The in-situ nasal gel was prepared to consume Carbopol as a gelling agent, Hypromellose (HPMC) as a thickening or thickness-imparting agent, and buffering agents to maintain pH. An assessment was conducted to determine the solubility, pH, rheological characteristics, consistency of content, adhesive properties to mucous membranes, gel strength, *in-vitro* release characteristics, the kinetics of release date, isotonicity, and sterility of the sample. **Results:** All formulations had a clear appearance with good gelling capacity, and drug content was found to be >87%. The pH values of the formulations were found to be acceptable, ranging from 6.2 ± 0.10 to 6.4 ± 0.44, and no irritation of the mucosal membranes was observed. The shearing character was found between 200-1400 at pH 6.4 and 2000-5500 cps at pH 7.4 when measured at 20 rpm. They also showed adequate gel strength of 14 ± 0.35 and mucoadhesion values ranging from 854 ± 0.33 dynes/cm2 to 5517 ± 1.88 dynes/cm^2, as well as sustained drug release. Based on these results, the optimal concentration range for both polymer and stand was determined to be between 0.775 and 0.800 for all parameters. Therefore, it can be concluded that in-situ nasal gel of LCH is a promising drug delivery system that could enhance bioavailability by overcoming first-pass metabolism.

INTRODUCTION:

Allergic Rhinitis: Allergic rhinitis (AR) is a prevalent and chronic type 2 inflammatory disorder that is heterogeneous in nature and has been present for a long duration [1, 2]. The incidence of AR increased daily, affecting a significant number of individuals worldwide [3, 4].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(5).2573-85

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.14(5).2573-85

The pathogenesis of AR is a complex process involving the interaction between environmental allergens, the immune system, and the nasal mucosa. Upon the entry of an allergen into system, is identified as a foreign substance by the immune system, which triggers an immune response [5, 6].

Immunoglobulin E (IgE) antibody production starts automatically when an allergen triggers the immune system, which attaches to the allergen and activates mast cells and basophils. These cells release various mediators, such as histamine and leukotrienes, that cause inflammation and swelling of the nasal mucosa. Consequently, these events result in the symptoms associated with allergic

rhinitis [7]. Various allergens like pollen, dust, animal dander, and mold cause allergic rhinitis (AR). Its symptoms include sneezing, nasal congestion, runny nose, itchiness of the nose, mouth, or throat, and watery eyes. These symptoms can range from mild to severe and may persist for days or weeks [8]. Diagnosing allergic rhinitis (AR) is typically based on the patient's medical history, symptoms, and physical examination. Sometimes, allergy testing may be conducted to identify the specific allergen causing the reaction [9, 10]. AR also shows the global impact on a person's health and economic condition [11]. Evidence shows that changes in climate, environmental exposure, family history, and lifestyle factors increase the chances of getting an allergic disorder [12, 13].

A strong association exists between asthma and allergic rhinitis, where many individuals diagnosed with allergic rhinitis also suffer from asthma, and vice versa [14]. Research estimates suggest that nearly 80% of individuals with asthma also experience allergic rhinitis. Research data shows allergic rhinitis increased theatrically daily in Europe (Danish), from 19 to 32% and for Americans 10 to 30%, respectively [15, 16].

Avoiding is the best treatment for AR. If medication is the preferred course of action, managing allergic rhinitis often involves utilizing antihistamines, nasal corticosteroids, decongestants, and immunotherapy as commonly employed treatments. Lifestyle changes such as keeping the home clean, avoiding tobacco smoke, and reducing exposure to pets can also help manage allergic rhinitis [17, 18]. H1 antihistamines are extensively used in reliving seasonal and perennial AR, urticaria, mild-moderate seasonal asthma, angioedema, *etc.* [19, 20]. Second-generation antihistamines are characterized by their high molecular weight, low lipid solubility, and reduced affinity for cerebral H1 receptors [21, 22]. It is also analyzed that whenever an accident happens, either road or air, excluding alcohol/drug, there is always first-generation H1-antihistaminic found in post-partum report [23, 24].

Levocetirizine: Levocetirizine hydrochloride (LCH) is a second-generation antihistamine used to cure AR, urticaria, and other allergic conditions. It comes in different dosage forms, such as tablets, oral solutions, and nasal sprays. In May 2007, the United States Food and Drug Administration (FDA) approved Levocetirizine, followed by a successful New Drug Application (NDA) submission [25]. Dr. Reddy's Laboratory has launched Levocetirizine tablets (5mg) and different doses. By blocking histamine, LCH can relieve AR indications and progress quality of life for people with allergies [26]. Levocetirizine, marketed as Xyzal®, is a second-generation antihistamine that Levocetirizine is the active R-enantiomer of cetirizine. Its chemical formula is C21H25ClN2O3, and its chemical name is 2-(2-{4-[(R)-(4-chlorophenyl) (phenyl) methyl] piperazin-1-yl} ethoxy) acetic Acid. It belongs to the piperazine class of medications [27] as shown below in **Fig. 1.**

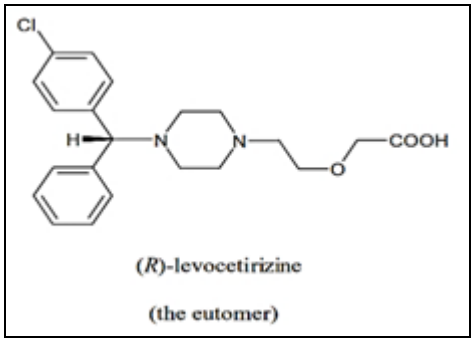


FIG. 1: CHEMICAL STRUCTURE OF LEVOCETIRIZINE

It is selective, potent, non-sedating, and acts as an inverse agonist Levocetirizine is a more potent and selective antagonist of the histamine H1 receptor [28, 29, 30, 31]. Levocetirizine is prescribed to manage various allergic conditions such as allergic rhinitis, atopic dermatitis, acute and chronic idiopathic urticaria, and insect bites and stings [32, 33]. Additionally, to treat hay fever, seasonal asthma accompanied by allergic rhinitis, and some respiratory infections (although no scientific evidence supports its use for the latter) [34, 35]. Also, have a large dose tolerance for antihistamine, antiangiogenic, and additional anti-inflammatory activities with no side effects on the cardiac system [36, 37]. Nasal spray of LCH was also developed. Rathanan *et al.* [38].

Nasal *In-situ* Gel: Nasal in-situ gel is a unique drug delivery system designed to undergo gelation *in-situ*, i.e., inside the nasal cavity, after administration in the liquid form. This type of preparation with polymer can form gel when

triggered by a specific condition like body temperature, which enables the drug to remain in the nasal cavity for longer, providing sustained drug release. Additionally, the gel has mucoadhesive properties, which allow it to adhere to the nasal mucosa and facilitates the drug's absorption [39].

The *in-situ* gel designed for nasal administration presents a promising avenue for managing diverse respiratory conditions such as AR, nasal congestion, and other related ailments. The advantages of this system include improved drug delivery, reduced dosing frequency, increased patient compliance, and reduced side effects. This formulation also increased permeation [40].

Different stimuli, such as changes in temperature, pH, or ions 41 can trigger gelation of in-situ gelling systems (ISGs). The nasal in-situ gel system enables a prolonged and sustained drug release, improving the holding period and bioavailability [42]. Carbopol is a commonly used polymer for in-situ nasal gel because it converts solution into viscid form at a low concentration when the pH is neutralized. It is a water-soluble polymer that provides mucoadhesive properties [43].

Hypromellose (HPMC) is another polymer commonly used in intra-nasal preparation, in addition to Carbopol. HPMC is a water-soluble polymer that forms a gel-like substance upon contact with aqueous fluids. Utilizing these polymers as viscosity boosters or gelling agents can broaden the rheological attributes of the gel, consequently leading to sustained drug delivery [44].

Artificial nasal fluid (ANF) is a solution designed to mimic fluid composition in the nasal chamber. The composition of ANF may vary depending on the specific application, but a commonly used composition is as follows:

- 150 ± 32 mM sodium (Na+)
- 41 ± 18 mM potassium (K+)
- 4 ± 2 mM calcium (Ca2+)
- pH 6

Other ions and compounds such as chloride (Cl-), bicarbonate (HCO3-), magnesium (Mg2+), and glucose may also be included in ANF, depending on the specific application [45].

EXPERIMENT:

Material: LCH was procured from GRANULE INDIA LIMITED, Tadi, Visakhapatnam, as a gift sample. Many additives used for the preparation of the in-situ nasal gel include Carbopol 941 (from LobaChemiePvt. Ltd., Mumbai), HPMC K15 (from LobaChemiePvt. Ltd., Mumbai), Benzalkonium chloride (from Ases chemicals works, Jodhpur), glycerine (from Ases chemicals works, Jodhpur), distilled water (prepared in-house), dialysis membrane (from Hi–Media, Mumbai), Whatman's filter paper-42 (from Whatman Int. Ltd, England), and other analytical/IP/equivalent grade chemicals and solvents. Equipment used includes a digital pH meter (Hanna, PHep), Brook field viscometer (book field LV DV-II+ pro), magnetic stirrer (Remi, 1MLH), and weighing balance (Adair Dutt-FX 200).

Preparation of Levocetirizine Hydrochloride Gel: The study used a full 3^2 factorial design to check the properties of two influencing variables, Carbopol 941 and HPMC K15, on the gel's properties. The main cause of developing the intra nasal gel preparation was to create a user-friendly aqueous formulation that can be easily self-administered and would undergo instant gelation on pH changes. Introductory trials were conducted to evaluate the gelation properties of Carbopol 941 at concentrations ranging from 0.4% to 0.8% w/v and the viscosity-enhancing properties of HPMC K15 at the same concentration range.

These concentrations were used to prepare nine different formulations (F1 to F9) of the LCH nasal *in-situ* gel. The levocetirizine drug was dissolved in distilled water to prepare the in-situ gel formulation. Separately, HPMC K15 was triturated with glycerine and mixed with buffer salt solution before hydrating. Carbopol 941 was then added to the solution and allowed to hydrate overnight. The solution was stirred at 500 RPM for 2 hours on a magnetic stirrer, and the drug was added with continuous stirring until thoroughly mixed. Distilled water is introduced to the solution to achieve the final volume, followed by a preservative. The pH of the solution was then adjusted to 4 using either sodium hydroxide or

hydrochloric acid. Upon administration, the solution rapidly gelled when it reached the nasal mucosal membrane, attributed to the pH alteration. The composition of various formulations of LCH was revealed in **Table 1.**

TABLE 1: THE COMPOSITION OF VARIOUS FORMULATIONS OF LEVOCETIRIZINE HYDROCHLORIDE

Group Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Levocetirizine Hydrochloride (g)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Carbopol 941 (% w/v)	0.4	0.4	0.4	0.6	0.6	0.6	0.8	0.8	0.8
HPMC K15M (% w/v)	0.4	0.6	0.8	0.4	0.6	0.8	0.4	0.6	0.8
Benzalkonium chloride (BKC) (%v/v)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Disodium hydrogen phosphate (% w/v)	0.68	0.68	0.68	0.68	0.68	0.68	0.68	0.68	0.68
Distilled water (q.s.)	100	100	100	100	100	100	100	100	100

Evaluation:

Physical Examination [46, 47, 48]: The color, homogeneity, and texture of the prepared LCH in-situ gel formulations were visually examined. The observations are presented in **Table 2.**

Measurement of pH using Digital pH Meter [49]: The pH of the In-Situ gel formulations was measured using a digital pH meter. To do this, 1gm of gel was dissolved in 100 ml of distilled water. The pH of each formulation was measured in triplicate, and the mean ± standard deviation (SD) was calculated. The observations are revealed in **Table 2.**

Rheologic Studies with Brookfield Viscosimeter [50, 51]: The rheology of the LCH In-Situ gel was assessed using a Brookfield viscometer with spindle 96 for the gel and spindle 62 for the solution, both before and after gelation).

The readings were noted down and the averages of three readings were calculated. The viscosity values of the LCH In-Situ gel formulations at pH 6.4 and pH 7.4 were recorded and are presented in **Table 2.**

Gelling Capacity [52]: It was determined by adding the formulation to simulated nasal fluid and evaluated. The observations are presented in **Table 2.**

Drug Content Determination [53]: To determine the drug quantity of the LCH In-Situ gel formulations, 1 ml of each formulation was accurately pipetted out and diluted with distilled water to up to 100 ml.

Then, a 5 ml aliquot of the diluted solution was withdrawn and further diluted with 25 ml of distilled water. The absorbance of LCH in each diluted solution was then measured at 231 nm. The drug quantity of each formulation was calculated using a standard calibration curve of LCH, and the results are presented in **Table 2.**

Measurement of Gel Strength [54]: To determine the gel strength of the nasal *in-situ* gel formulations, A volume of 100 ml was measured using a graduated cylinder, and the sample 35 g used was positioned on top of the gelled formulation. The time noted in seconds to penetrate 5 cm into the cylinder was recorded as the gel strength. The gel strength values for all the formulations are presented in **Table 2.**

Determination of Mucoadhesive Strength [55]: Using tape, two glass slides were fixed with a piece of egg membrane. 50mg of gel was placed on one slide, then under the height-adjustable pan. The second slide was fixed inverted position and held against the first slide for 2 minutes to ensure intimate contact. The weight was essential for separation was then measured. The mucoadhesive strength was determined, as mentioned in **Table 2.**

$$\text{Mucoadhesive strength (dynes/cm}^2\text{)} = mg/A$$

Where: m= gm wt. for detachment, g = acceleration 980cm/s^2,A = Exposed are of membrane

Drug Release [56, 57, 58]: The *in-vitro* issue of medicine from the *in-situ* gel formulations was evaluated using two-chamber diffusion cells with a dialysis membrane of molecular weight cut off 1200-1400 KDa. The diffusion cell had a diameter of 1.5 cm and a capacity of 20 ml, with an upper cylindrical compartment open from above and a diffusion membrane at its base. Two milliliters of *in-situ* gel loaded with the drug were placed in the donor section, and 20 ml of phosphate buffer pH 6.4 was located in the receptor section.

The temperature was maintained at 37°C ± 0.5°C during the experiment, and the content was stirred at 50 rpm using a magnetic stirrer. Subsequently, samples of 1 ml were extracted from the receiver chamber initially after 30 minutes and subsequently at hourly intervals for up to 6 hours, followed by replacement with a fresh medium of equal volume.

These extracted samples were appropriately diluted and subjected to UV spectrophotometric analysis at 231 nm for drug quantification. The *in-vitro* release was conducted for a total duration of 6 hours. The drug release profiles obtained from the in-situ gel formulations were compared with the theoretical release profile, as presented in **Table 3.**

RESULTS AND DISCUSSION: The physical characteristics of the prepared Levocetirizine Hydrochloride gelling systems, such as texture, homogeneity, and color, were found satisfactory for all formulations, as shown in **Table 2.** The pH of the nasal mucosal membrane in a normal physiological state ranges from 5.5 to 6.5. However, in the case of A R, the pH of the nasal mucosal membrane increases to 7.2-8.3 [59]. The physical characteristics of the prepared gelling system of Levocetirizine Hydrochloride were found to be good, including texture, homogeneity, and colorlessness. The pH of all gels was within the acceptable range of 6.2±0.10 to 6.4±0.44 for nasal mucosa tolerance. Due to hydrogen bonding, lower pH values (<7) provide better mucoadhesive properties and longer retention in the nasal chamber.

The drug amount of the various formulations were within the range of 87.1 ± 0.049% to 109.76 ± 0.041%. The gel strength was found between 14 ± 0.35 secs to 71 ± 0.55secs, while the Mucoadhesive Strength was observed between 854 ± 0.33 dynes/cm2 to 5517 ± 1.88 dynes/cm^2.

The viscosity values were found between 200-1400 cps at pH 6.4 and 2000-5500 cps at pH 7.4, at 20 rpm. The average effect of the concentration of the suspending or thickening agent (HPMC K15M) and the gelling agent (Carbopol 941) of the prepared LCH nasal *in-situ* gel at 20 rpm at pH 6.4 and pH 7.4 are shown in **Fig 2.**

The analysis of viscosity data through ANOVA revealed that an increase in the concentration of HPMC K15M from 0.4% to 0.8% resulted in an insignificant increase in viscosity at pH 6.4 (P=0.57; df 2,6; F=0.61; Fcrit=5.14).

Likewise, HPMC K15M different concentrations from 0.5% to 1.5% resulted in an insignificant increase in viscosity at pH 7.4 (P=0.55; df 2, 6; F=0.64; Fcrit=5.14).

However, when Carbopol 941, different concentrations from 0.4% to 0.8% resulted in a substantial rise in viscosity at pH 6.4 (P=0.015; df 2, 6; F=8.97; Fcrit=5.14). Similarly, when Carbopol 941concentraion increased from 0.4% to 0.8% resulted in a substantial rise in viscosity at pH 7.4 (P=0.010; df 2, 6; F=10.56; Fcrit=5.14).

Physical Examination, pH, Gel Strength, Gelling Capacity, Rheology and Mucoadhesive Strength:

TABLE 2: PHYSICAL CHARACTERISTICS OF PREPARED GELLING SYSTEM OF LEVOCETIRIZINE HYDROCHLORIDE

Formulation Code	Appearance	pH*	Drug content(%) *	Gelling capacity	Viscosity (cP)*(6.4)	rheology (cP)*(7.4)	Gel strength (s)*	Mucoadhesive strength (Dynes/cm^2)*
F1		6.2±0.10	87.1 ± 0.049	+	329 ± 10	2087 ± 10	14 ± 0.35	854 ± 0.33
F2		6.4±0.10	103.64 ± 0.03	++	338 ± 5	2200 ± 11	20 ± 0.18	1211 ± 1.21
F3	Transparent	6.3±0.06	99.22 ± 0.079	++	364 ± 8	2450 ± 11	27 ± 0.37	1568 ± 0.36
F4		6.3±0.12	106.67 ±0.091	++	542 ± 5	2425 ± 21	26 ± 1.29	1452 ± 1.32
F5		6.3±0.21	106.14 ±0.052	+++	681 ± 6	3110 ± 11	35 ± 1.26	2092 ± 0.21
F6		6.2±0.21	109.76 ±0.041	+++	879 ± 3	3956 ± 11	51 ± 0.39	3763 ± 1.37
F7		6.3±0.21	104.36 ±0.039	+++	730 ± 7	3757 ± 10	50 ± 1.55	3696 ± 0.56
F8		6.3±0.26	107 ± 0.011	+++	981 ± 6	4616 ± 10	65 ± 0.18	4510 ± 1.31
F9		6.4±0.26	109.57 ± 0.03	+++	1294 ± 7	5100 ± 10	71 ± 0.55	5517 ± 1.88

*Average of three determinations. Note: Few minutes of application, the +gel dissolves rapidly, while the ++gel shows immediate gelation and remains stable for a few hours. The +++gel shows immediate gelation and remains stable for extended periods.

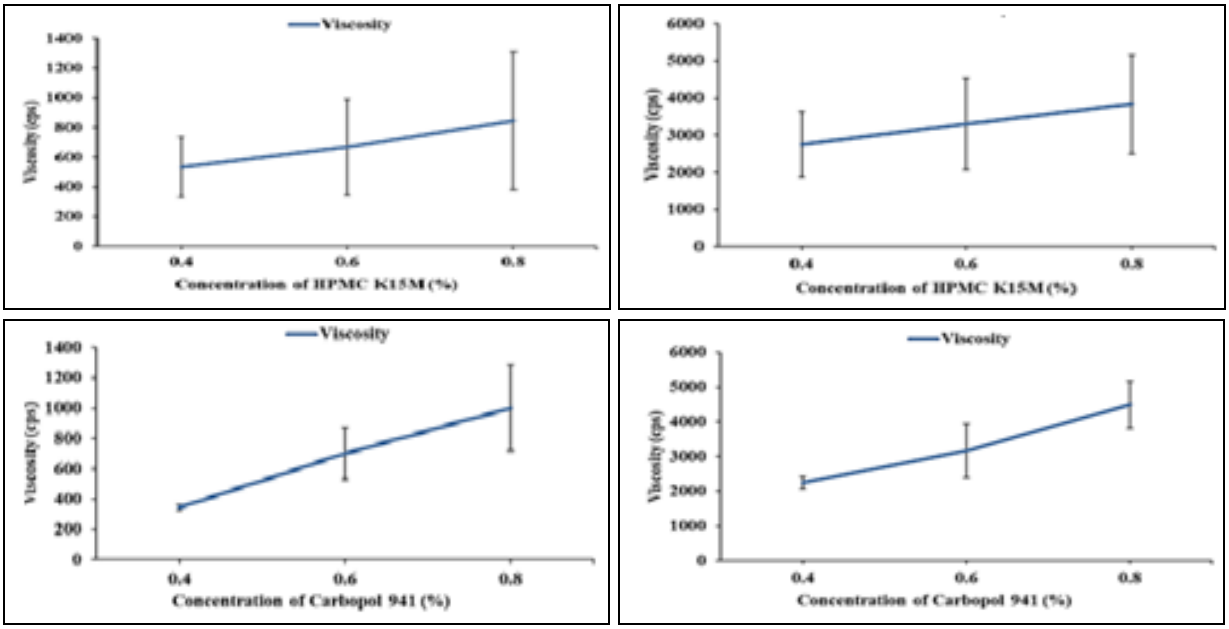


FIG. 2: AVERAGE CONCENTRATION-DEPENDENT EFFECT OF HPMC K15M AND CARBOPOL 941 ON VISCOSITY AT 20 RPM AT PH 6.4, 7.4 RESPECTIVELY

***In-vitro* Release Study:** The descending order of LCH release from all *in-situ* gel formulations was as follows: F1 > F2 > F3 > F5 > F6 > F4 > F8 > F7 > F9.

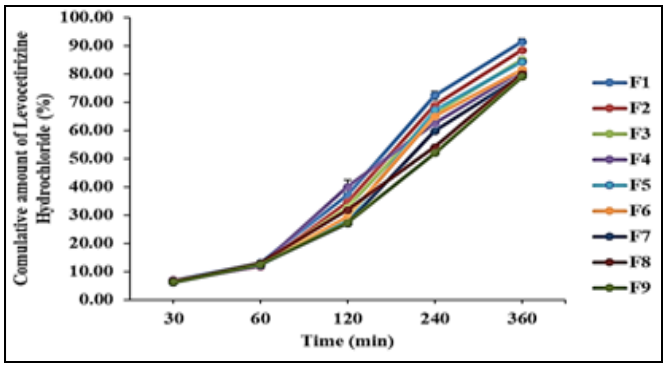
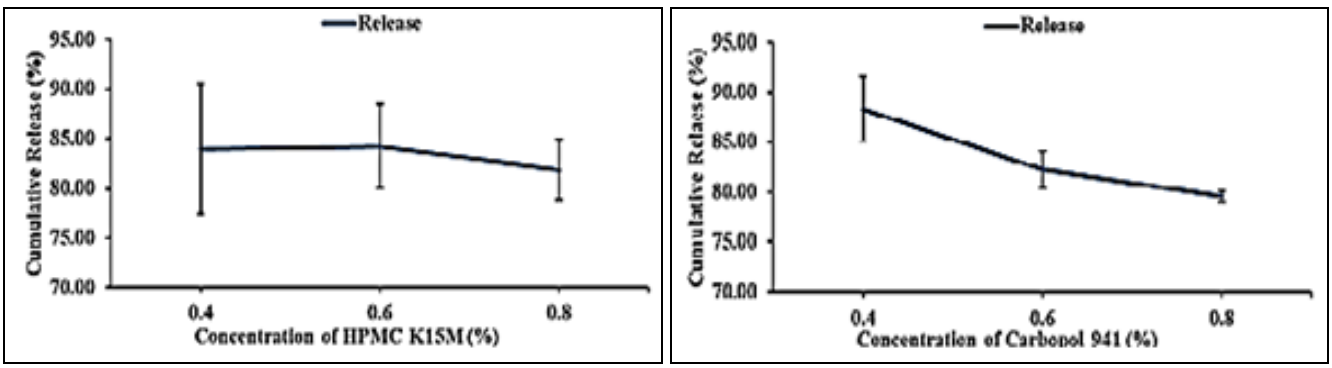


FIG. 3: *IN-VITRO* RELEASE OF LEVOCETIRIZINE HYDROCHLORIDE FROM DIFFERENT FORMULATIONS

The release of LCH after 6 hours was 91.45%, 88.42%, 85.06%, 84.34%, 81.5%, 80.98%, 80.05%, 79.46%, and 79.07% for formulations F1 to F9, respectively, as illustrated in **Fig. 3.**

To compare the release contour of Levocetirizine Hydrochloride Nasal in-situ gel with a theoretical profile, the similarity factor *f*2 was used. Formulations F1 to F9 had similarity factor values of 43.32, 47.37, 51.80, 51.71, 52.44, 55.75, 64.95, 67.91, and 80.23, respectively.

This indicates that except for the first two formulations, the rest had a similar release profile to the desired theoretical profile, with a similarity factor value of more than 50. Average concentration-dependent effect of HPMC K15M and Carbopol 941 on *in-vitro* release of levocetirizine hydrochloride from different formulations at 360 and 240 min respectively in **Fig. 4.**



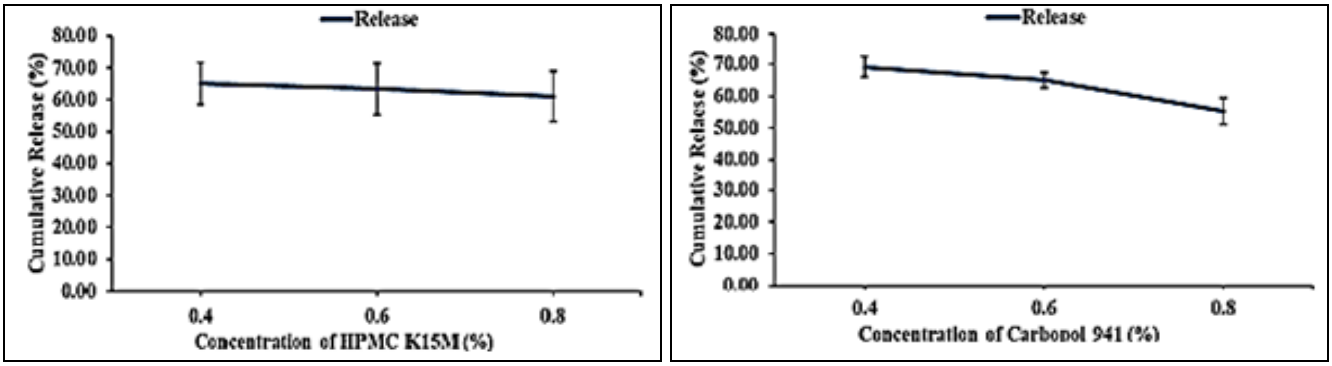


FIG. 4: AVERAGE CONCENTRATION-DEPENDENT EFFECT OF HPMC K15M AND CARBOPOL 941ON IN-VITRO RELEASE OF LEVOCETIRIZINE HYDROCHLORIDE FROM DIFFERENT FORMULATIONS AT 360 AND 240 MIN, RESPECTIVELY

TABLE 3: *IN-VITRO* DRUG RELEASE OF *IN-SITU* GEL ALONG WITH THEORETICAL RELEASE PROFILE

Time (min)	Cumulative amount (%)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	TP
30	6.97 ± 0.098	7.03 ± 0.129	6.26 ± 0.131	6.51 ± 0.099	6.78 ± 0.071	6.45 ± 0.03	6.24 ± 0.041	6.55 ± 0.03	6.3 ± 0.019	6.25
60	13.16 ± 0.098	11.87 ± 0.233	12.27 ± 0.059	12.14 ± 0.049	12.34 ± 0.099	12.82 ± 0.03	12.57 ± 0.039	13.05 ± 0.011	12.59 ± 0.041	12.5
120	37.04 ± 0.822	34.73 ± 0.974	32.76 ± 0.301	40.07 ± 2.357	28.21 ± 0.411	29.53 ± 0.301	27.09 ± 0.342	31.9 ± 0.301	27.35 ± 0.114	25
240	72.41 ± 1.429	68.86 ± 0.114	66.02 ± 0.712	62.6 ± 0.57	67.21 ± 0.197	65.03 ± 0.197	59.83 ± 0.228	54.16 ± 0.197	51.93 ± 0.114	50
360	91.45 ± 0.994	88.42 ± 0.301	85.06 ± 0.891	80.98 ± 0.748	84.34 ± 0.411	81.5 ± 0.603	79.46 ± 0.197	80.05 ± 0.197	79.07 ± 0.395	75
f_2 factor	43.32	47.37	51.80	51.71	52.44	55.75	64.95	67.91	80.23	

The release date at 360 minutes was analyzed using ANOVA, which revealed that an increase in the concentration of HPMC K15M from 0.4% to 0.8% resulted in an insignificant (P=0.80; df 2, 6; F=0.22; Fcrit=5.14) decrease in drug liberation. On the other side, when Carbopol 941concentraion increased from 0.4% to 0.8% resulted in a significant (P=0.006; df 2, 6; F=13.23; Fcrit=5.14) decrease in drug liberation. The release date at 240 minutes was analyzed using ANOVA, revealing that an increase in the concentration of HPMC K15M from 0.4% to 0.8% resulted in an insignificant (P=0.81; df 2,6; F=0.20; Fcrit=5.14) decrease in drug release. On the other hand, when Carbopol 941 concentration increased 941 from 0.4% to 0.8% resulted in a significant (P=0.005; df 2,6; F=14.00; Fcrit=5.14) decrease in drug release.

Kinetic Treatment of Release Data: Table 4 shows the release kinetics of different formulations obtained by fitting the raw dissolution data of drug passage in solution into various release models, including zero-order, first-order, Higuchi's, Hixson Crowell's, and Korsmeyer's Peppas equations.

TABLE 4: THE RELEASE KINETICS OF VARIOUS FORMULATIONS

Formulation Code	Release kinetics-Model Fitting						
	Co-relation Coefficient for the model					Korsemeyer-Peppas	
	0 - order R% vs T	1 - order log R% vs T	Highuchi R% vs $T^{1/2}$	Hixon-Crowell ($100^{1/3}$ - $R\%^{1/3}$) vs T	Korsemeyer-Peppas M_t/M_∞ vs T	k	n
F1	0.9888	0.9228	0.9950	-0.9537	0.9888	0.0017	1.0861
F2	0.9906	0.9297	0.9941	-0.9582	0.9906	0.0017	1.0796
F3	0.9917	0.9270	0.9950	-0.9585	0.9917	0.0015	1.0931
F4	0.9796	0.9004	0.9937	-0.9334	0.9796	0.0018	1.0607
F5	0.9902	0.9438	0.9890	-0.9683	0.9902	0.0017	1.0650
F6	0.9904	0.9342	0.9925	-0.9629	0.9904	0.0018	1.0601
F7	0.9956	0.9419	0.9924	-0.9706	0.9956	0.0018	1.0503
F8	0.9971	0.9314	0.9942	-0.9648	0.9971	0.0021	1.0144
F9	0.9997	0.9465	0.9898	-0.9769	0.9997	0.0020	1.0191

Formulation F5, F7, F8 and F9 the suitable model was Zero Order model with correlation coefficient of 0.9902, 0.9956, 0.9971 and 0.9997, respectively.

Data Analysis:

Multiple Regression Analysis: Multiple linear regression analysis (MLRA) was used to generate a second-order statistical model that included interaction and polynomial terms for all the response variables. The following equations were derived to describe the relationship between drug release (Y) and concentration of Carbopol 941 (X_1) and HPMC K15M (X_2):

Model for Drug Release:
At 6 Hours:

$Y_{360} = 115.63-93.84X_1+12.81X_2+41.17X_1^2-33.76X_2^2+37.46X_1X_2$

($R^2 = 0.944$)

Model for Drug Release:
At 4 Hours:

$Y_{240} = 59.79+53.55X_1+8.97X_2-68.62X_1^2-10.97X_2^2-9.46X_1X_2$

($R^2 = 0.890$)

The model exhibited a good fit for the responses as specified by the high R2 values. The amount of Carbopol 941 (X1) and HPMC K15M (X2) significantly influenced drug release.

Response Surface Methodology [60]: The 3-dimensional response surface for percentage drug release at 6 hours and 4 hours is shown in **Fig. 5** and the 2D contour plot is in **Fig. 6**.

The 3-dimensional response surface for the viscosity of the gel at pH 7.4 and pH 6.4 is shown in **Fig. 7**. The contour plot showing the impact of the varying concentration of Carbopol 941 and HPMC K15M on the viscosity of Levocetirizine Hydrochloride *in-situ* nasal gel at pH 7.4 (a) and pH 6.4 (b) at 20 RPM is revealed in **Fig. 8.**

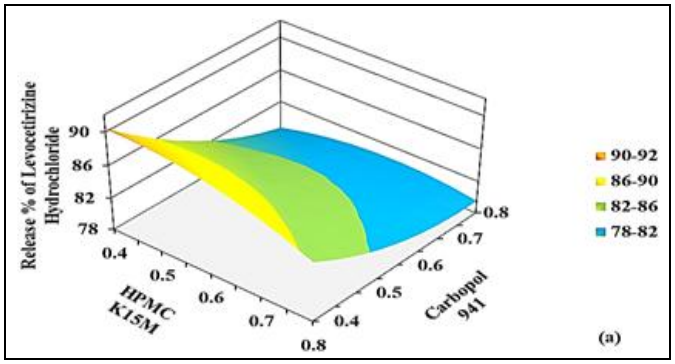


FIG. 5: THREE-DIMENSIONAL RESPONSE SURFACE PLOTS PRESENTING THE CONCENTRATION-DEPENDENT EFFECT OF CARBOPOL 941 AND HPMC K15M ON THE PERCENT DRUG RELEASE OF LCD

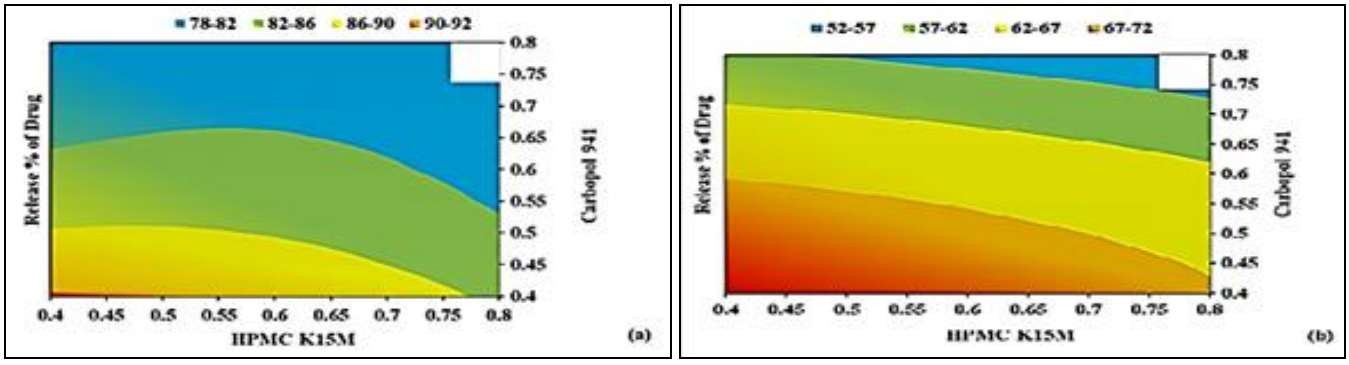


FIG. 6: CONTOUR PLOT PRESENTING CONCENTRATION-DEPENDENT EFFECT OF CARBOPOL 941 AND HPMC K15M ON RELEASE OF LCH FROM *IN-SITU* NASAL GEL AT 6 HOURS (A) AND AT 4 HOURS (B)

The following equations were derived to describe the relationship between Gel Viscosity (Y) and concentration of Carbopol 941 (X_1) and HPMC K15M (X_2):

Model for Gel Viscosity:
At 7.4 pH 20 RPM:

$Y_{7.4} = 2114.66-4197.50X_1-588.33X_2+5112.50X_1^2-325X_2^2+6125X_1X_2$

($R^2 = 0.981$)

Model for Gel Viscosity:
At 6.4 pH 20 RPM:

$Y_{6.4} = 375.58+501.25X_1-1893.75X_2-700X_1^2+525X_2^2+3306.25X_1X_2$

($R^2 = 0.999$)

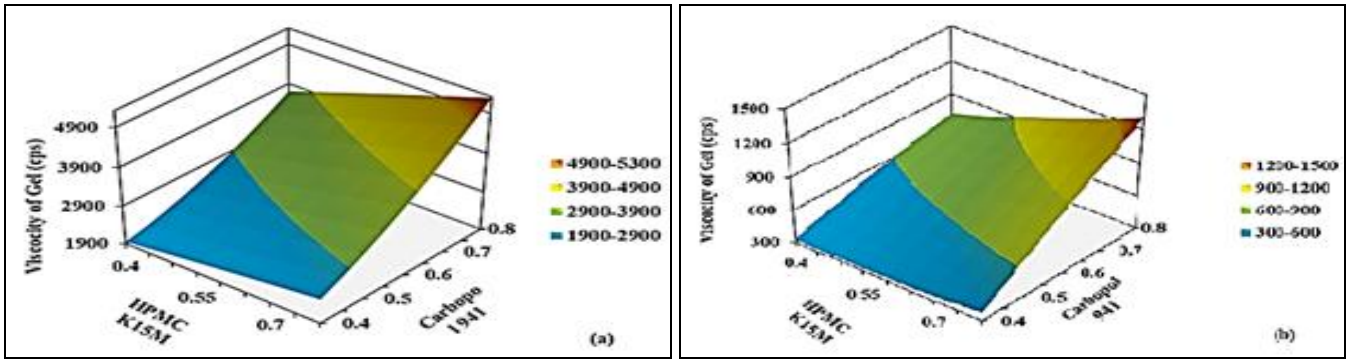


FIG. 7: THREE-DIMENSIONAL RESPONSE SURFACE PLOTS SHOWING CONCENTRATION-DEPENDENT EFFECT OF CARBOPOL 941 AND HPMC K15M ON VISCOSITY OF LEVOCETIRIZINE HYDROCHLORIDE *IN-SITU* NASAL GEL AT 7.4 PH (A) AND AT 7.4 PH (B) 20 RPM

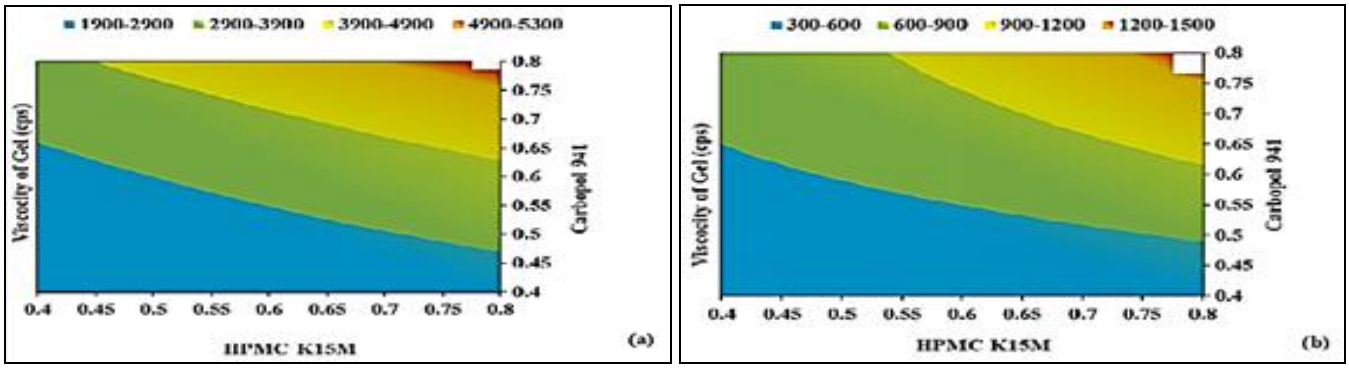


FIG. 8: CONCENTRATION-RESPONSE CONTOUR PLOT OF CARBOPOL 941 AND HPMC K15M ON VISCOSITY OF LEVOCETIRIZINE HYDROCHLORIDE *IN-SITU* NASAL GEL AT 7.4 PH (A) AND AT 7.4 PH (B) 20 RPM

Design Space [61]:

Building of Design Space: The proposed design space comprises the overlap region of ranges for percentage drug release (6 hours and 4 hours) for concentration is 0.765-0.800 for both Carbopol 941 and HPMC K15M.

Check Point Formulation: Validation of Model for Design Space: A formulation was prepared with X_1: amount of Carbopol 941 i.e. 0.775 and X_2: amount of HPMC K15M i.e. 0.775. The *in-situ* nasal gel was then subjected to release studies to assess drug release at 6 hours and 4 hours. The actual and predicted drug release values were compared by determining % bias or residual. The formula for the calculation of % bias/residual is as follows:

% Bias/Residual = (Predicted value – Actual value)/Predicted value × 100

The predicted response using the regression equation, the actual response and residuals are presented in **Table 5.**

TABLE 5: RESULTS OF EVALUATION OF THE CHECKPOINT FORMULATION

Parameter	Actual response (A)	Predicted response (P)	Residuals (P-A)	% Residuals [(P-A)/P x 100]
Drug release at 6 hours	80.23 %	79.796%	0.434 %	0.54 %
Drug viscosity at 7.4 pH	5015 cps	4960 cps	55 cps	1.10 %

The close resemblance between the actual and the predicted response indicates the validity of the generated models.

Stability Studies of the Optimized Batch as per ICH Guidelines: Q1 "Stability Testing of New Drug Substances and Product" [62]:

Accelerated Stability Testing: The optimized checkpoint formulation was filled in plastic dropping bottle container and stored at 40°C temperature and 75% R.H. for 4 weeks. Samples were withdrawn at 7-day time intervals and evaluated. *In-vitro* release of the intra nasal gel preparation of LCH from optimized check point formulation stored under accelerated stability conditions shown in **Fig. 9.**

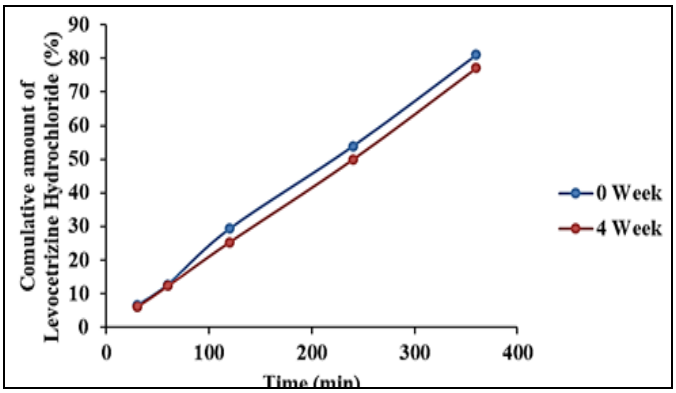


FIG. 9: *IN-VITRO* RELEASE OF THE NASAL GEL OF LCH FROM OPTIMIZED CHECKPOINT FORMULATION STORED UNDER ACCELERATED STABILITY CONDITION

Approximation of Shelf Life: Using the Bracket method, on subjecting the value into the equation:

t_s = exp [20/0.00199(1/298-1/313)] x 120

= days as 527.21 days or 17.57 months or 1.44 yrs.

RESULTS AND DISCUSSION: The optimized formulation demonstrated good physical stability as no discoloration or physical change occurred after storage. All parameters met the acceptance criteria.

Gel Sterility Test [63]: Fluid thioglycollate medium (FTG) for anaerobic/aerobic bacteria incubated at 30º to 35º while Soybean-casein digest medium (SBCD) for the fungi and aerobic bacteria at 20º to, 25º recpectively.

Outcomes: Three different culture media were prepared as test, control, and negative. In the test (FTG and SBCD), 1 ml of the gel was mixed aseptically and incubated for 7 days. Similarly, in the control (FTG and SBCD) medium, normal tap water introduce to cross-check the observation. A negative was also prepared in which nothing was to be added.

After 7 days, there is growth in "control" as the FTG became more intense red and SBCD precipitated, while no growth was observed in the test and negative.

Test for Isotonicity [64]: The isotonicity of nasal fluid is equivalent to that of a 0.9% sodium chloride solution, which is the same as the isotonicity value of blood.

The optimized formulation is mixed with little blood droplets. It was observed microscopically at a magnification of 45x, and the shape of the blood cells was compared. No ruptures occurred in the red blood cells.

CONCLUSION: A complete 32-factorial design was used to examine the impact of two self-determining variables, namely the amount of Carbopol 941 and HPMC K14M, on the percentage of the drug issue, viscosity, and mucoadhesive strength. After that, optimization was carried out.

To address the challenges associated with other drug dosage forms, such as limited availability of medicines in the nasal mucosal area, adding water-soluble polymers to increase the viscidness of the dosage form is one solution. Another approach involves increasing drug residence time by transforming polymeric solutions into *in-situ* gel due to pH and physiological factors. Levocetirizine has been confirmed to have a stronger and more long-lasting effect than other antihistamines like loratadine or cetirizine.

Additionally, Levocetirizine has a lower risk of causing drowsiness and other side effects, which can be a significant concern for people who need to remain alert and focused during the day also has a quick response, which means that it starts working more quickly to relieve allergy symptoms. The use of pH triggered in-situ gelling system for LCH provides several advantages, such as improved residence time, sustained drug release, and targeted drug discharge to the nasal mucosal membrane. The incorporation of Carbopol 941 and HPMC

K14M in the formulation facilitates gel formation upon coming in contact with the physiological pH of the nasal mucosal membrane, which aids in extending drug availability and reducing dosing frequency. The study underscores the significance of fine-tuning the polymer concentrations employed in the formulation for achieving the desired viscosity and drug liberation profile. In conclusion, the in-situ gel system developed in this study exhibits the potential for enhancing therapeutic outcomes and promoting patient adherence in managing AR.

ACKNOWLEDGEMENT: The authors thank the associate professor, B N College, for encouraging and supporting the manuscript's preparation.

CONFLICTS OF INTEREST: The Authors declared no conflict of interest.

REFERENCES:

1. Greiner, Alexander N., Peter W. Hellings, Guiseppina Rotiroti and Glenis K: Scadding. Allergic rhinitis. The Lancet 378 2011; 378(9809): 2112-2122.
2. Zhang, Yuan, Feng Lan and Luo Zhang: Advances and highlights in allergic rhinitis. Allergy 2021; 76(11): 3383-3389.
3. Wheatley, Lisa M and Alkis Togias: Allergic rhinitis. New England Journal of Medicine 2015; 372(5): 456-463.
4. Linton, Sophia, Alyssa G. Burrows, Lubnaa Hossenbaccus and Anne K. Ellis: Future of allergic rhinitis management. Annals of Allergy, Asthma & Immunology 2021; 127(2): 183-190.
5. Lee P and Mace S: An approach to allergic rhinitis. Allergy Rounds 2009; 1: 1.
6. Nur Husna S. M, Tan HTT, Md Shukri N, Mohd Ashari NS and Wong KK: Allergic rhinitis: a clinical and pathophysiological overview. Frontiers in Medicine 2022; 9: 940.
7. Barnesa and Peter J: Pathophysiology of allergic inflammation. Immunological Revie 2011; 242(1): 31-50.
8. Small P, Frenkiel S, Becker A, Boisvert P, Bouchard J, Carr S, Cockcroft D, Denburg J, Desrosiers M, Gall R and Hamid Q: Rhinitis: A Practical and Comprehensive Approach to Assessment and Therapy. Journal of Otolaryngology 2007; 36.
9. Meltzer, Eli O, Michael S. Blaiss, M. Jennifer Derebery, Todd A. Mahr, Bruce R. Gordon, Ketan K. Sheth, A. Larry Simmons, Mark A. Wingertzahn and John M: Boyle. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. Journal of Allergy and Clinical Immunology 2009; 124: 43-70.
10. Nathan, Robert A. The burden of allergic rhinitis.In Allergy & Asthma Proceedings 2007; 28(1).
11. Avdeeva, Klementina S., Sietze Reitsma and Wytske J: Fokkens. Direct and indirect costs of allergic and non-allergic rhinitis in the Netherlands. Allergy 2020; 75(11): 2993.
12. Alkotob SS, Cannedy C, Harter K, Movassagh H, Paudel B, Prunicki M, Sampath V, Schikowski T, Smith E, Zhao Q and Traidl-Hoffmann C: Advances and novel developments in environmental influences on the development of atopic diseases. Allergy 2020; 75(12): 3077-3086.
13. McKeever TM, SA Lewis, C. Smith, J. Collins, H. Heatlie, M. Frischer and R: Hubbard. Siblings, multiple births, and the incidence of allergic disease: a birth cohort study using the West Midlands general practice research database Thorax 2001; 56(10): 758-762.
14. Anastasio E, Brambilla I, Caffarelli C, Chini L, Ciprandi R and De Vittori V: The treatment of allergic rhinitis in asthmatic children and adolescents: practical outcomes from the real-world "ControL'Asma" study. allergy Clinical Immunology 2021; 53(3): 143–5.
15. Schuler Iv CFm and Montejo JM. Allergic Rhinitis in Children and Adolescents. Immunol Allergy Clin North Am 2021; 41(4): 613–25.
16. Wang, Han-Rui, Shi-Zhuang Wei, Xiao-Yu Song, Yao Wang, Wen-Bin Zhang, Chao Ren, Ya-KuiMou and Xi-Cheng Song: IL-1β and Allergy: Focusing on Its Role in Allergic Rhinitis. Mediators of Inflammation 2023.
17. Sur, Denise KC and Stephanie Scandale: Treatment of allergic rhinitis.American Family Physician 2010; 81(12): 1440-1446.
18. Taglialatela, Maurizio, Henk Timmerman and Lucio Annunziato: Cardiotoxic potential and CNS effects of first-generation antihistamines. Trends in Pharmacological Sciences 2000; 21(2): 52-56.
19. Howarth PH: Assessment of antihistamine efficacy and potency." Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology 1999; 29: 87-97.
20. Terada, Tetsuya and Ryo Kawata: Diagnosis and treatment of local allergic rhinitis pathogens 2022; 11(1): 80.
21. Yanai, Kazuhiko and Maria Beatrice Passani: Eds. The Functional Roles of Histamine Receptors. Springer Nature 2022; 59.
22. Church MK, Maurer M, Simons FER, Bindslev-Jensen C, Van Cauwenberge P, Bousquet J, Holgate ST and Zuberbier T: Risk of first-generation H1-antihistamines: a GA2LEN position paper. Allergy 2010; 65(4): 459-466.
23. Hindmarch I, Z. Shamsi, N. Stanley and DB: Fairweather. A double-blind, placebo-controlled investigation of the effects of fexofenadine, loratadine and promethazine on cognitive and psychomotor function. British Journal of Clinical Pharmacology 1999; 48(2): 200-206
24. Chen and Chen: "Physicochemical, pharmacological and pharmacokinetic properties of the zwitterionic antihistamines cetirizine and levocetirizine." Current Medicinal Chemistry 2008; 15(21): 2173-2191.
25. Launches Levocetirizine tablets in US - Dr. Reddy Laboratories Ltd. 2011.
26. Devillier, Philippe, Nicolas Roche and Christophe Faisy: Clinical pharmacokinetics and pharmacodynamics of desloratadine, fexofenadine and Levocetirizine: a comparative review. Clinical pharmacokinetics 2007; 47: 217-230.
27. Camelo-Nunes and Inês Cristina: New antihistamines: a critical view. "Journal of Pediatrics 2006; 82: 173-180.
28. 29. Gillard, Michel, Christy Van Der Perren, Nicole Moguilevsky, Roy Massingham, and Pierre Chatelain. Binding characteristics of cetirizine and Levocetirizine to human H1 histamine receptors: Contribution of Lys191and Thr194. Molecular Pharmacology 2002; 61(2): 391-399.
29. Tzanetos, Douglas B., John M. Fahrenholz, Theresa Scott, and Kristina Buchholz: Comparison of the sedating effects of Levocetirizine and cetirizine: a randomized, double-

blind, placebo-controlled trial. Annals of Allergy, Asthma & Immunology 2011; 107(6): 517-522.
30. Sin, Betul and Alkis Togias: Pathophysiology of allergic and nonallergic rhinitis. Proceedings of the American Thoracic Society 2011; 8(1): 106-114.
31. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, Lang DM, Nicklas RA, Oppenheimer J, Portno JM and Randolph CC: The diagnosis and management of rhinitis: an updated practice parameter. Journal of Allergy and Clinical Immunology 2008; 122(2): 1-84.
32. Wang DY, F. Hanotte, C. De Vos and P. Clement: Effect of cetirizine, Levocetirizine, and dextrocetirizine on histamine-induced nasal response in healthy adult volunteers. Allergy 2001; 56(4): 339-343.
33. Horak, Friedrich and Ursula Petra Stübner: Comparative tolerability of second generation antihistamines. Drug Safety 1999; 20: 385-401.
34. Ridout, Sally M and Syed M. Tariq: "Cetirizine overdose in a young child." The Journal of Allergy and Clinical Immunology 1997; 6(99): 860-861.
35. Albash, Rofida, Rania Moataz El-Dahmy, Mohammed IA Hamed, Khaled M. Darwish, Abdulrahman M. Alahdal, Amira B. Kassem and Abdurrahman M. Fahmy: Repurposing levocetirizine hydrochloride loaded into cationic ceramide/phospholipid composite (CCPCs) for management of alopecia: central composite design optimization, *in-silico* and *in-vivo* studies."Drug Delivery 2022; 299(1): 2784-2795.
36. Pagano, Cinzia, Luana Perioli and Maurizio Ricci: Novel Approaches in Nasal *in-situ* Gel Drug Delivery. In Nasal Drug Delivery: Formulations, Developments, Challenges, and Solutions, Cham: Springer International Publishing 2023; 235-252.
37. El Taweel MM, Aboul-Einien MH, Kassem MA and Elkasabgy NA: Intranasal zolmitriptan-loaded bilosomes with extended nasal mucociliary transit time for direct nose to brain delivery. Pharmaceutics 2021; 13(11): 1828.
38. Bashir, Rabiah, Mudasir Maqbool, Irfat Ara and Mehrukh Zehravi: An Insight into Novel Drug Delivery System: In Situ Gels. CELLMED 2021; 11(1): 6-1.
39. Keller, Lea-Adriana, Olivia Merkel and Andreas Popp: Intranasal drug delivery: Opportunities and toxicologic challenges during drug development. Drug Delivery and Translational Research 2021: 1-23.
40. Zahir-Jouzdani, Forouhe, Julian Dominik Wolf, Fatemeh Atyabi and Andreas Bernkop-Schnürch: *In-situ* gelling and mucoadhesive polymers: why do they need each other?.Expert Opinion on Drug Delivery 2018; 15(10): 1007-1019.
41. Thakur, Rakesh and Abhishek Sharma: An Overview of Mucoadhesive Thermoreversible Nasal Gel. Asian Journal of Pharmaceutical Research and Development 2021; 9(4): 158-168.
42. Khatri, Upasana, Sunil Saini and Meenakshi Bharkatiya: "Pharmaceutical Considerations of Nasal In-Situ Gel As A Drug Delivery System." Asian Journal of Pharmaceutical Research and Development 2021; 9(3): 94-103.
43. Upasana, Khatri, Kamal Singh Rathore, Sunil Saini and Bharkatiya Meenakshi: Formulation and evaluation of ketorolac tromethamine using 32 factorial design. Research Journal of Pharmacy and Technology 2020; 13(6): 2556-2562.
44. Lorin, Martin I, Pureza F. Gaerlan and Irwin D: Mandel. Quantitative composition of nasal secretions in normal subjects. The Journal of Laboratory and Clinical Medicine 1972; 80(2): 275-281.
45. Bechgaard E and Anni Nielsen: Bioavailability of bromhexine tablets and preliminary pharmacokinetics in humans. Biopharmaceutics & Drug Disposition 1982; 3(4): 337-344.
46. Chien YW: A textbook of Anatomy and physiology of the nose. In Nasal Systemic Drug Delivery: Drugs and the Pharmaceutical Sciences. New York, Marcel Decker: 1989.
47. Nair, Anroop B, Jigar Shah, Shery Jacob, Bandar E. Al-Dhubiab, NagarajaSreeharsha, Mohamed A. Morsy, Sumeet Gupta, Mahesh Attimarad, Pottathil Shinu and Katharigatta N. Venugopala: Experimental design, formulation and in vivo evaluation of a novel topical in situ gel system to treat ocular infections. PloS one 2021; 16(3): 0248857.
48. Cho, Eunsook, Hyesun Gwak and Inkoo Chun: Formulation and evaluation of ondansetron nasal delivery systems. International Journal of Pharmaceutics 2008; 349(1-2): 101-107.
49. Pallavi and Kukkamudi: Formulation and evaluation of proliposomal gels of naproxen using various grades of hpmc polymers 2021.
50. Simões, Ana, Margarida Miranda, Catarina Cardoso, Francisco Veiga and Carla Vitorino: "Rheology by design: A regulatory tutorial for analytical method validation." Pharmaceutics 2020; 19(9): 820.
51. Talasaz, Azita HH, Ali A. Ghahremankhani, Shadi H. Moghadam, Mazda R. Malekshahi, Fatemeh Atyabi and Rassoul Dinarvand: *In-situ* gel forming systems of poloxamer 407 and hydroxypropyl cellulose or hydroxypropyl methyl cellulose mixtures for controlled delivery of vancomycin. Journal of Applied Polymer Science 2008; 109(4): 2369-2374.
52. Nair AB, Chaudhary S, Shah H, Jacob S, Mewada V, Shinu P, Aldhubiab B, Sreeharsha N, Venugopala KN, Attimarad M and Shah J: Intranasal delivery of darunavir-loaded mucoadhesive in situ gel: Experimental design, *in vitro* evaluation, and pharmacokinetic studies. Gels 2022; 8(6): 342.
53. Sherafudeen, Sheri Peedikayil and Prasanth Viswanadhan Vasantha: Development and evaluation of in situ nasal gel formulations of loratadine. Research in Pharmaceutical Sciences 2015; 10(6): 466.
54. Majithiya Rita J, Pradip K. Ghosh, Manish L. Umrethia and Rayasa SR Murthy: Thermoreversible-mucoadhesive gel for nasal delivery of sumatriptan. AAPS Pharmscitech 2006; 7: 80-86.
55. Uppuluri, Chandra Teja, Punna Rao Ravi and Avantika V. Dalvi: Design, optimization and pharmacokinetic evaluation of Piribedil loaded solid lipid nanoparticles dispersed in nasal in situ gelling system for effective management of Parkinson's disease. International Journal of Pharmaceutics 2021; 606: 120881.
56. Peppas NA: Analysis of Fickian and non-Fickian drug release from polymers. Pharmaceutica Acta Helvetiae 1985; 60 (4): 110-111.
57. Knoester PD, Jonker DM, R. T. M. Van Der Hoeven, T. A. C. Vermeij, P. M. Edelbroek, G. J. Brekelmans and De Haan GJ: Pharmacokinetics and pharmacodynamics of midazolam administered as a concentrated intranasal spray. A study in healthy volunteers. British Journal of Clinical Pharmacology 2002; 53(5): 501-507.
58. England RJA, Homer JJ, Knight LC and Ell SR: Nasal pH measurement: a reliable and repeatable parameter. Clinical Otolaryngology & Allied Sciences 1999; 249(1): 67-68.
59. Vicente, Gemma, A. Coteron, M. Martinez and J. Aracil: Application of the factorial design of experiments and

response surface methodology to optimize biodiesel production. Industrial Crops and Produc 1998; 8(1): 29-35.
60. Mason, Robert L, Richard F. Gunst and James L. Hess: Statistical design and analysis of experiments: with applications to engineering and science. John Wiley & Sons 2003.
61. Guideline IHT: Stability testing of new drug substances and products. Q1A (R2), current step 2003; 4: (1–24).
62. Gupta, Pallavi, and Khushwant S. Yadav. Formulation and evaluation of brinzolamide encapsulated niosomal *in-situ* gel for sustained reduction of IOP in rabbits." Journal of Drug Delivery Science and Technology 2022; 63: 103004.
63. Tai, Junhu, Munsoo Han, Dabin Lee, Il-Ho Park, Sang Hag Lee and Tae Hoon Kim: "Different methods and formulations of drugs and vaccines for nasal administration." Pharmaceutics 2022; 14(5): 1073.

How to cite this article:
Khatri U, Bharkatiya M and Saini S: Formulation and evaluation of pH trigger nasal in-situ gel of levocetirizine hydrochloride for localized treatment of allergic rhinitis. Int J Pharm Sci & Res 2023; 14(5): 2573-85. doi: 10.13040/IJPSR.0975-8232.14(5).2573-85.