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Research Article

Formulation Development and Characterization of Levocabastine Hydrochloride Ophthalmic Suspension

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Abstract

Background: In the present study, an attempt was made to develop and evaluate the ophthalmic suspension containing levocabastine hydrochloride.

Objective: The current research objective's rationale was to develop and assess ophthalmic suspension containing antihistamine to improve corneal penetration with corneal tissues and obtain therapeutic efficiency. Recently, ophthalmic drug delivery has become the modern pharmaceutical design standards and intensive research for achieving better drug product effectiveness, reliability, and safety. Topical medication by ocular drug delivery will continue to account for the largest share (up to 90%).

Methods: The prepared ophthalmic suspension had a minimum concentration of preservative preparation in appropriate packaging material. FTIR and UV spectrum of API was found as per specification. The individual IR spectra of the pure drug and the combination spectra of the drugs and other excipients indicated no interaction between API and other excipients than the infrared spectrum of the pure drug as all available group frequencies were present.

Results: The pH of all formulations was satisfactory in the range of 6.0-8.0; thus, there would be no irritation to the patient upon administration of the formulation. The particle size analysis revealed that the particles were in range, and all the formulations showed ideal surface morphology. All the formulations showed osmolality within the range, i.e., 250-500 mOsm/kg.

Conclusion: Finally it was confirmed that formulations of antihistamine ophthalmic suspension remained more stable at ambient temperature (25°C) and relative humidity (40%) as compared to other stability conditions as per ICH guidelines.

Keywords: Corneal Penetration; FTIR; Osmolality; Ambient Temperature; Relative Humidity

Abbreviations

API: Active Pharmaceutical Ingredient; FTIR: Fourier Transform Infrared Spectroscopy; EDTA: Disodium Edentate

Introduction

The eye is the most exciting organ due to its drug disposition characteristics. Generally, topical drug application is the method of choice under most circumstances because of its convenience and safety for ophthalmic chemotherapy. The biggest drawback to a formulator is to circumvent (bypass) the eye's protective barriers, negatively impacting the tissues [1]. The advancement of newer, more sensitive diagnostic techniques and novel therapeutic agents provides ocular delivery systems with high therapeutic efficacy [2]. Conventional ophthalmic formulations like the solution, suspension, and ointment have many disadvantages, which result in low bioavailability of the drug in the eyes. The basis of designing a therapeutic system is to achieve an optimal drug concentration at the desired site for the requisite time [3]. Ocular disposition and elimination of a therapeutic agent depends on its physicochemical properties and the relevant ocular anatomy and physiology [4,5]. Therefore, a successful design of a drug delivery system requires a combined researched knowledge of the drug molecules and the constraints offered by the ocular route of administration. The present research work aims to develop and evaluate ophthalmic suspension containing levocabastine hydrochloride to improve corneal penetration.

- To formulate a stable suspension system using polymers HPMC 2906.
- To investigate the impact of varying concentrations of polymer HPMC 2906 on the viscosities of formulations.
- Idea about selecting suitable primary packaging material for ophthalmic suspension incompatibility, with the product, most appropriate packaging material was also determined.
- The product was also evaluated for stability, potency, toxicity, and safety under the accelerated temperature and humidity conditions.

Drug profile

Levocabastine hydrochloride is primarily used for the treatment allergic conjunctivitis. Hence there is a need for a formulation with better corneal permeation.

- **Chemical formula:** $C_{26}H_{29}FN_2O_2$
- **Class** : Phenylpiperidines
- **Molecular Weight**: 420.519
- **Category**: H_1 –receptor antagonist (II nd generation topical antihistamines)
- **Colour**: White colour powder.
- **Solubility**: Practically insoluble in water, sparingly soluble in methanol.

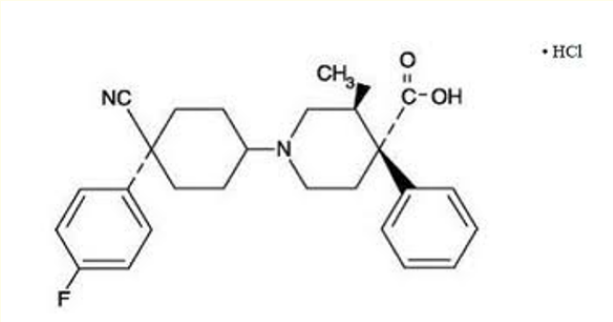

Figure 1: Chemical structure of Levocabastine Hydrochloride.

Materials and Methods

Levocabastine hydrochloride was received as a gift sample from ALP Pharma, Beijing. Benzalkonium chloride, Disodium edetate, hydroxypropyl methylcellulose 2906 (Merck, Germany), Polysorbate80, Propylene Glycol (Sigma-Aldrich).

Method of preparation

The initial process consisted of preparing the water for injection (WFI), which was purged with nitrogen for about 30 minutes. The required amount of hypermellose was then added slowly to a beaker containing WFI and subjected to a continuous stirring process for about 45 minutes in order to obtain an exact solution of the Polymer Phase. Simultaneously on the other end, the buffer phase preparation was initiated in another beaker by the progressive addition of disodium edentate (EDTA), Phosphate buffers, propylene glycol, Benzalkonium chloride with stirring till all the excipients are entirely dissolved. The buffer phase was then filtered by suction filter through a 0.45µ PVDF filter. The intermediate pH of the solution was measured after the addition of each of the excipients.

Finally, the Active Pharmaceutical ingredient slurry phase was prepared by adding a weighed amount of levocabastine hydrochloride to a solution of polysorbate 80 in WFI and stirred for three hours. Polymer phase was added to the buffer phase with stirring for 20 min continuous pH measurement. API slurry phase was added to the above phase and homogenized by the Polytron for about 15mins at 2000rpm. Then the final pH was checked and adjusted as depicted in table 1.

Name of the Ingredients	Formulation Batches					
	BATCH 1	BATCH 2	BATCH 3	BATCH 4	BATCH 5	BATCH 6
Levocabastine hydrochloride	0.54%	0.54%	0.54%	0.54%	0.54%	0.54%
Benzalkonium chloride	0.025%	0.020%	0.015%	0.015%	0.010%	0.015%
Propylene glycol	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Polysorbate 80	0.50%	0.40%	0.30%	0.25%	0.15%	0.10%
Disodium phosphate (ANHYDROUS)	0.86%	0.86%	0.86%	0.86%	0.86%	0.86%
Sodium dihydrogen phosphate monohydrate	0.53%	0.53%	0.53%	0.53%	0.53%	0.53%
Disodium edetate	0.015%	0.015%	0.015%	0.015%	0.015%	0.015%
Hydroxypropyl Methyl cellulose 2906	0.40%	0.30%	0.10%	0.15%	0.20%	0.25%
Hydrochloric Acid	Adjust pH	Adjust pH	Adjust pH	Adjust pH	Adjust pH	Adjust pH
Sodium hydroxide	Adjust pH	Adjust pH	Adjust pH	Adjust pH	Adjust pH	Adjust pH
Water from Injection	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 1: Optimized trial batches of with varied strength of preservatives, polysorbates and polymer ratios.

Calibration curve

Calibration curve of API in ethanol was prepared and analyzed in the UV range at a maximum wavelength of 262nm.

FT-IR spectroscopy

API and polymer interactions were assessed by FT-IR spectroscopy. FT-IR spectra of pure drug levocabastine hydrochloride and its mixture with EDTA, disodium phosphate, and dihydrogen phosphate were recorded in IR Prestige-21, ShimadzuEmit Co.LTD, Japan).

Appearance, pH, viscosity, osmolality

Were determined as per the standard procedure.

Particle size

Optimum particle size of suspensions was determined using Mastersizer Malvern, UK.

In-vitro diffusion studies

The *in vitro* release of the drug from the respective formulations was studied by using the cellophane membrane method, i.e., using the altered USP XXIII dissolution testing model. The dissolution medium used was simulated tear fluid freshly prepared (pH 7.4). The cellophane membrane, which was previously soaked overnight in the simulated dissolution medium, was tied to one end of a designed glass cylinder with specified (open at both ends and of 5 cm diameter). 1ml volume of the formulation was accurately pipetted into this assembly. The cylinder was firmly adhered to the metallic driveshaft and suspended in 50 ml of dissolution medium maintained at 37 ± 1°C so that the membrane just touched the receptor medium surface. The dissolution medium was stirred at ten blinks per minute using a magnetic stirrer. Aliquots, each of 1-ml volume, were withdrawn at 15 minutes intervals and replaced by an equal volume of the receptor medium [6].

Stability study

Stability testing were performed for formulation batch six as per ICH guidelines 40°C± 2°C/ NMT 25% RH 25°C ± 2°C/40%RH.

Results and Discussion

- **Appearance:** All formulations were found to be off white color suspension. Terminal sterilization by filtration gives sterile suspension, but after sometimes form hard cake at the bottom of containers, after shaking cake was dispersed.
- **Particle size:** The particle size distribution of the drug sample was analyzed, and Batch 6 found not more than 10 microns, but after autoclaving of API, the particle size was increased.

Particle size	d(0.1)	d(0.5)	d(0.9)
BATCH6	0889nm	2.534nm	7.454nm
BATCH6	1.021nm	6.557nm	9.548nm

Table 2: Reported particle size of pure drug and formulation.

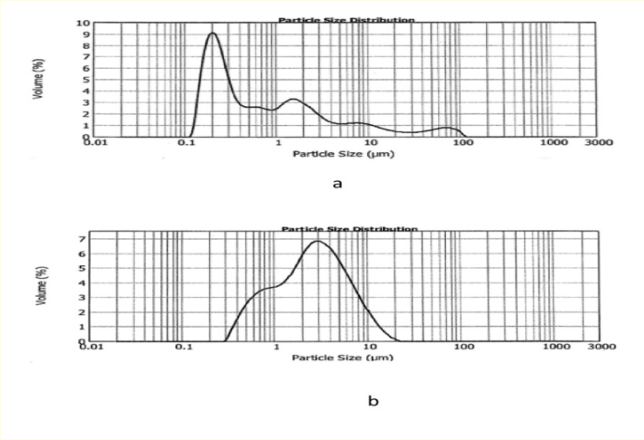

Figure 2: (a). Particle size of Pure drug of levocabastine hydrochloride. (b) Particle size of the ophthalmic suspension of levocabastine hydrochloride.

FTIR and pH

The pH of all formulations was found to be satisfactory and was in the range of 6-8. Sterilization by filtration and autoclaving had no effect on formulations. The FTIR spectra showed no interactions between the excipients and pure drug as depicted in figure 3.

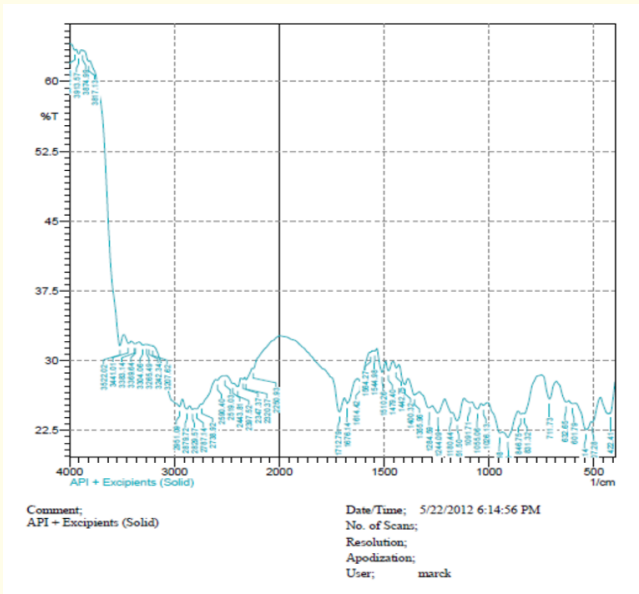

Figure 3: IR spectra of API and excipients.

Viscosity

Generally, viscosity values in the range of 1-10 cps significantly improve the contact time in the eye. Higher viscosity values offer no significant advantage and have a tendency to leave a noticeable residue on the lid margin.

Osmolality

The osmolality value for the formulations was obtained by using an advanced osmometer, model 3250. The value of each formulation is compared with the reported value, and select the best one. The osmolality range for ophthalmic suspension is 250-500 mOsm/kg as the reference product showed the osmolality in this above range.

Diffusion studies

In vitro diffusion showed improved permeation of drug across cellophane membrane using Franz diffusion cell.

Time(mins)	Absorbance at 262nm	Concentration (µg/ml)	Drug release(mg/50ml)	% Drug release	% Cumulative Drug release
15	0.031	1.24	0.62	12.40	12.40
30	0.063	2.52	1.26	25.20	25.44
45	0.096	3.84	1.92	38.40	38.90
60	0.130	5.20	2.60	52.32	52.56
75	0.165	6.60	3.30	66.56	67.25
90	0.202	8.08	4.04	80.40	81.32
105	0.221	8.84	4.42	88.40	90.56
120	0.240	9.60	4.80	96.23	97.36

Table 3: *In-vitro* Diffusion studies data.

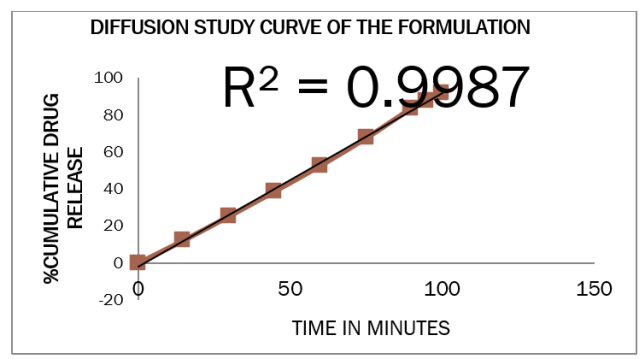

Figure 4: Drug release time profile curve.

Stability studies

The optimized formulation batch 6 showed no significant changes in evaluation parameters during the stability study of 6 months.

Conclusion

The ophthalmic suspension of levocabastine hydrochloride is been prepared successfully with improved corneal penetration, effective drug release and stability because of judicious combination of HPMC 2906 , Propylene glycol and polysorbate 80 (batch 6) combined with homogenization in order to treat the condition of allergic conjunctivitis globally. This research work can be further explored by performing *in-vivo* studies in future in order to establish the irritancy properties of the formulation.

Description	White color Suspension , filled in three piece container				
Stability conditions	Initial	40°C ± 2°C/NMT 25% RH		25°C ± 2°C/NMT 40 % RH	
Test parameters	1Month	2 Month	3 Month	4Month	6 Month
Assay (%)	99.3	97.1	98.6	98.1	97.3
Preservative Content (%)	98.6	98. 2	97.8	97.9	98.4
Viscosity (cps)	5.59	5.46	5. 51	5.47	5.57
Osmolality(mOsm)	238	320	310	280	276
Particle Size distribution	4.54	4.13	3.43	4.47	3.52

Table 4: Stability studies data of the formulation for Batch No.6.

Conflict of Interest

The authors have no conflict of interest.

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