

Original Research Article

Impact of preferred orientation and strain on Olopatadine HCl by using XRD technique.

Abstract:

This research article investigates the impact on the crystal structure of Olopatadine HCl using an X-ray diffractometer. During the stability study, the diffractogram obtained shows a significant shift in 2 Theta, which can be attributed to the presence of strain and preferred orientation within the crystal lattice. The study reveals that the strain is caused by lattice defects and impurities, while the preferred orientation can be attributed to the method of preparation adopted. The results indicate that the crystal structure of Olopatadine HCl is complex and requires further investigation to fully understand its properties. The findings of this study could be used to optimise the synthesis protocol and improve the material properties for various applications.

Keywords: Preferred orientation, Olopatadine HCl, XRD, IR

INTRODUCTION

Olopatadine HCl is a potent histamine H₁ receptor antagonist used for the treatment of allergic conjunctivitis and rhinitis. [1] Olopatadine hydrochloride exerts a wide range of pharmacological actions, such as histamine H₁ receptor antagonist action, chemical mediator suppressive action, and eosinophil infiltration suppressive action [2]. Olopatadine hydrochloride 0.1% ophthalmic solution (Patanol[®]) was introduced to the market in Japan in October 2006. [3] Oral administration of Olopatadine at doses of 0.03 mg/kg or higher

inhibited the symptoms of experimental allergic skin responses, rhinoconjunctivitis, and bronchial asthma in sensitised guinea pigs and rats. [4]

The preferred orientation and strain effect in organic molecules can have a significant impact on their properties and behaviour [5]. Preferred orientation refers to the tendency of the molecules to align themselves in a particular way. This can be due to various factors such as intermolecular forces, crystal packing, and electronic interactions. For example, in a crystal lattice, molecules may preferentially align themselves in a way that minimises steric hindrance or maximises hydrogen bonding interactions. This preferred orientation can have negligible impact on the molecules of physical properties, such as melting point, boiling point, and solubility [6]. Strain effects in organic molecules arise from distortions in the molecular geometry or bond angles. This can be due to the presence of bulky groups [7]. Understanding the crystal structure of Olopatadine HCl is crucial in the development of effective drug formulations. [8] In this research article, we present the XRD Diffractogram of Olopatadine HCl, which exhibits a significant 2θ shift due to the phenomenon of 'strain' and 'preferred orientation'. [9] The diffraction peaks have been analysed and correlated with the crystal structure of Olopatadine HCl. Our study provides valuable information regarding the crystal habits of drug formulations and highlights the importance of considering the 'strain' and 'preferred orientation' phenomena in the analysis of the XRD Diffractogram [10, 11].

MATERIAL

Olopatadine HCl was used which is in-house manufactured in Indoco Remedies Ltd, Mumbai, India.

METHODS

1. IR

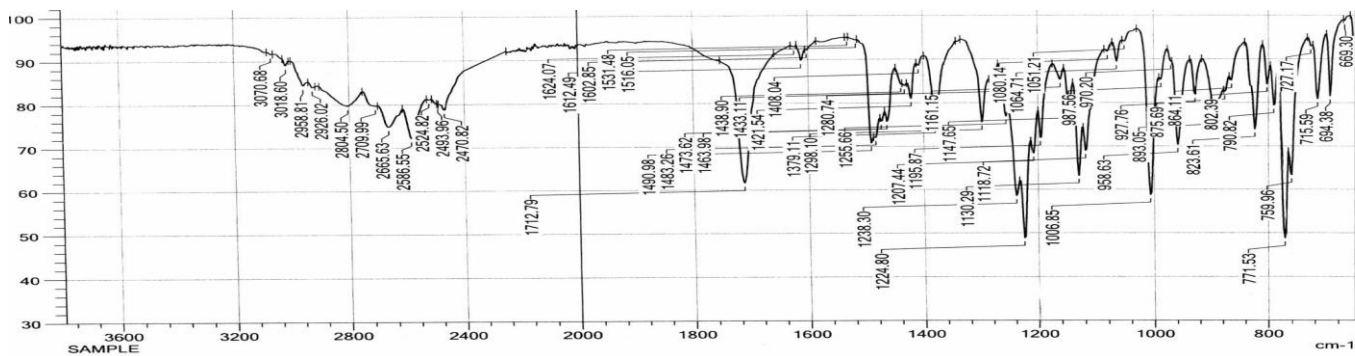
IR spectroscopy was carried out using the instrument Affinity I-S from Shimadzu, working with the software Lab Solution. Approximately 2 mg of sample was placed on the ATR crystal surface of diamond, and spectra were obtained in the range of 650 cm^{-1} to 3800 cm^{-1} .

Preparation of Sample

1. Infrared Spectroscopy

Approximately 1-2 mg of sample was placed on the ATR diamond crystal and spectra were obtained in the range from 650 cm^{-1} to 3800 cm^{-1} .

Fig-1 Infrared Spectroscopy of Olopatadine HCl



2. XRDP

Powder X-Ray Diffraction PANalytical X'Pert Pro from Malvern PANalytical, with Cu-K radiation ($\lambda = 1.54 \text{ \AA}$) at 40 kV, 45 mA moving through a nickel filter used to carry out the PXRD study. In continuous scan mode, data was collected using a step size of 0.0167113° and a time per step of 50.165 for an angular range 2θ of 2°C to 40°C . Approximately 300 mg of powder was taken; samples were prepared by using a back loading holder, and then samples were analysed.

Fig-2 XRD Diffractogram of Olopatadine HCl

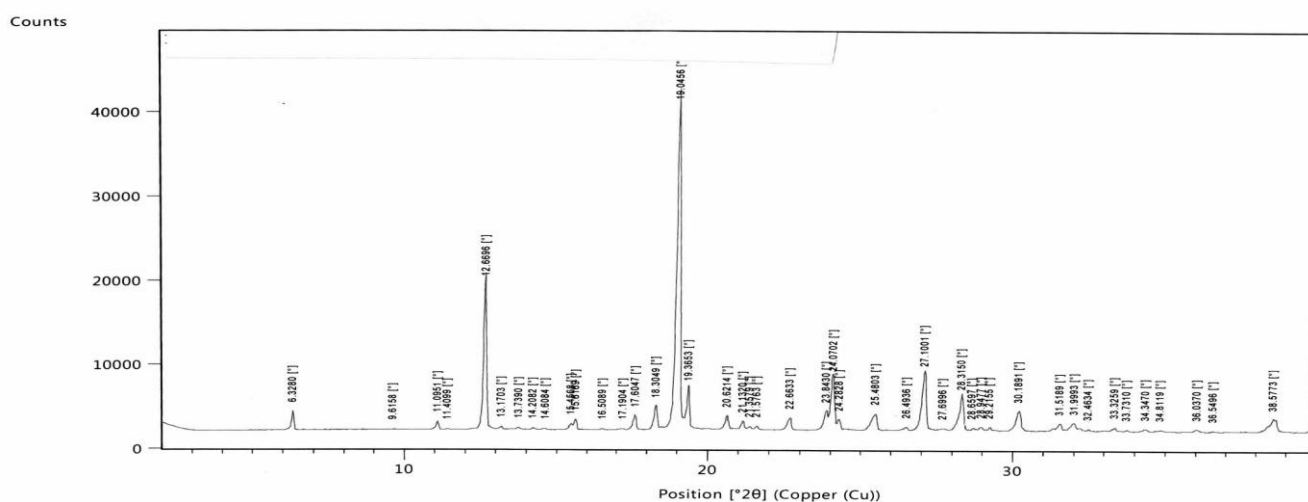
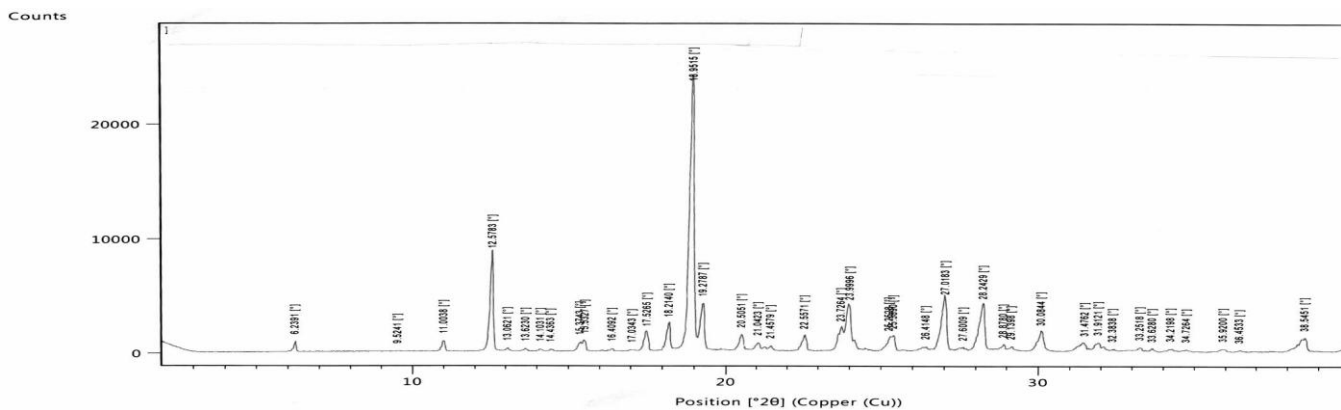


Fig-3 XRD Diffractogram of Olopatadine HCl with slightly left toward



RESULTS AND DISCUSSION

Table-1. 2θ values

Standard 2θ values (±)	Observed 2θ values	Difference
6.4539	6.2391	-0.21
11.2354	11.0038	-0.23
12.7912	12.5783	-0.21
17.7447	17.5265	-0.21
18.4392	18.2140	-0.23
19.1694	19.2787	0.11
20.7698	20.5051	-0.26
22.7974	22.5571	-0.24
23.9866	23.9996	0.01
27.2352	27.0183	-0.22
28.4610	28.2429	-0.22
30.3217	30.0844	-0.24

Olopatadine HCl from the same batch was incepted for a stability study. Diffractogram spectra were shifted towards the left side.

For the polymorphism study of API, powder XRD is preferred. In this technique of XRD:

Presence of uniform (macro) and non-uniform (micro) strains, which results in peak shift and peak broadening.

Olopatadine HCl exhibits Form (I). Also, during the shelf-life establishment period, no change in the XRD pattern or variation in 2Theta values is noticed. And there is no effect on the IR spectrophotometer.

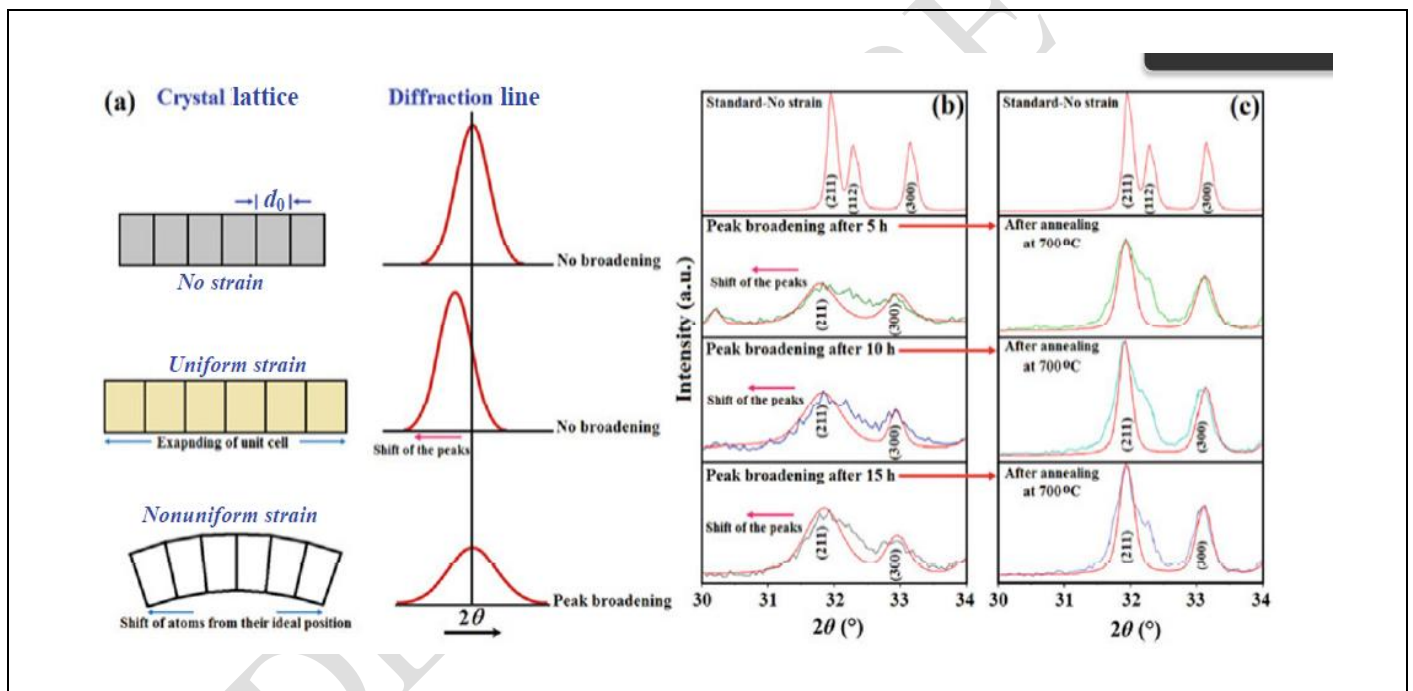
Low intensity of 2 Theta values: which results in increasing plane indices (higher angles in the pattern), the intensity of the peak goes down and leads to minor peak broadening.

It is a very commonly observed phenomenon. This effect is likely to occur due to the nature of the product within the sample. The phenomenon of presence of uniform and non-uniform strains' and low intensity of 2 Theta values' is possible because the particles will have different sizes and shapes.

The Pattern in all the analyses is similar, without any additional or abnormal peaks. However, in the diffractogram, a minor shift in the '2q values' and a change in the intensity (i.e., low) of the 2 θ values' are observed.

Due to the presence of uniform and non-uniform strains, the spacing of reflecting planes becomes larger than d_0 (d -spacing is defined as inter-atomic spacing) and the diffraction line shifts, leading to peak shift and peak broadening with low intensity of '2 θ values'.

Fig: 4: Effect of strain on XRD patterns



Presence of a uniform tensile strain at right angles, the spacing of reflecting planes becomes larger than d_0 (d -spacing is defined as inter-atomic spacing) and the diffraction line shifts. It is accompanied by the simultaneous presence of uniform and non-uniform strains which result in peak shift and peak broadening [11].

In the presence of uniform and non-uniform strain and low intensity of the 2 Theta Values effect, this leads to peak shifting and broadening issues.

In the case of powder XRD, the solid stability sample is analysed, and the phenomenon of uniform and non-uniform strain effects is possible because of the particles different sizes and shapes. This uniform strain effect is likely to occur due to the expanding of the unit cell, which resulted in the shifting of the peak to the left. It was seen that the XRD diffractogram pattern in all the analyses is similar without any additional or abnormal peaks, which rules out the change in polymorph. However, in the diffractogram, a minor shift in the '2 θ values' is observed. In the presence of a uniform tensile strain at right angles, the spacing of reflecting planes becomes larger than d_0 (d -spacing is defined as inter-atomic spacing), and the diffraction line shifts, resulting in a shifting of the peak. This will be generated within a sample of the analysis.

During this repeat analysis, when the particles in a sample are compacted, it will help to reduce the uniform and strain effects during XRD analysis. By compacting the sample, the particles are forced into random orientations, reducing or eliminating the uniform and non-uniform strain effects. The result is tabulated as below:

Table-2. 2 θ values

Standard 2θ values (\pm)	Observed 2θ values	Difference
6.4539	6.3217	-0.13
11.2354	11.0883	-0.15
12.7912	12.6640	-0.13
17.7447	17.6041	-0.14
18.4392	18.2839	-0.16
19.1694	19.0386	-0.13
19.5133	19.3561	-0.16
20.7698	20.6232	-0.15
22.7974	20.6651	-0.13
23.9866	23.8309	-0.16
24.2136	24.2691	0.06
27.2352	27.0928	-0.14
28.4610	28.3169	-0.14
30.3217	30.1774	-0.14

After taking precautionary measures (i.e., Compacting the sample specimen, which helps to reduce the uniform and non-uniform strains and low intensity of the 2 Theta values' effect during XRD analysis), the sample was found to be complying with specification. Also, such types of effects were not found during this particular analysis.

Conclusion:

The XRD diffractogram pattern in all the analyses is similar without any additional or abnormal peaks. A minor shift in peak with low intensity of 2Theta values' is observed, and this can be assigned to the phenomenon of uniform strains.

In the case of powder XRD, the phenomenon of uniform and non-uniform strain effects is possible because the particles have different sizes and shapes.

In the presence of a uniform tensile strain at right angles, the spacing of reflecting planes becomes larger than d_0 , and the diffraction line shifts to the lower angles, resulting in a shifting of the peak.

In the initial analysis, a low intensity value of 2q values effect was noticed, the observed intensity was about 25000, and peak boarding was observed.

There were no additional or abnormal peaks upon comparison of the diffractogram of the analysis.

Based on the above review and evaluation, during stability, some of the sample may acquire strain, which leads to strain effects and results in peak shifting and boarding, and this confirms that there is no change in polymorphism.

If any solid sample is analysed, the Presence of *uniform and varying strains* is possible because of the particles different sizes and shapes. This phenomenon is relevant for Olopatadine HCl API due to its nature as a crystal.

REFERENCES

1. Tamura, T., Sato, H., Miki, I., Suzuki, K., Ohmori, K., & Karasawa, A. (2003). *Effects of orally administered olopatadine hydrochloride on the ocular allergic reaction in rats. Allergology*
2. Uchio, Eiichi. "Treatment of allergic conjunctivitis with olopatadine hydrochloride eye drops." *Clinical Ophthalmology* 2.3 (2008): 525-531.
3. Eugene McLaurin, Mark Bergmann, Abhijit Narvekar, Adeniyi Adewale, Paul Gomes, Gail Torkildsen. (2017) *Pooled analysis of two studies evaluating efficacy and safety of olopatadine hydrochloride 0.77% in patients with allergic*

conjunctivitis. *Clinical Ophthalmology* 11, pages 1089-1097. *International*, 52(2), 77-83

4. Ohmori, K., Hayashi, K. I., Kaise, T., Ohshima, E., Kobayashi, S., Yamazaki, T., & Mukouyama, A. (2002). Pharmacological, pharmacokinetic and clinical properties of olopatadine hydrochloride, a new antiallergic drug. *The Japanese Journal of Pharmacology*, 88(4), 379-397.
5. Robinson, Ian, and Ross Harder. "Coherent X-ray diffraction imaging of strain at the nanoscale." *Nature materials* 8.4 (2009): 291-298.
6. Abramowitz, R., & Yalkowsky, S. H. (1990). Melting point, boiling point, and symmetry. *Pharmaceutical research*, 7, 942-947.
7. Brown, Herbert C. "Chemical effects of steric strains." *Journal of the Chemical Society (Resumed)* (1956): 1248-1268. Nobre, Thatyane M., et al. "Interactions of bioactive molecules & nanomaterials with Langmuir monolayers as cell membrane models." *Thin Solid Films* 593 (2015): 158-188. Wiberg, K. B. (1986). The concept of strain in organic chemistry. *Angewandte Chemie International Edition in English*, 25(4), 312-322.
8. Bunjes, Heike, and Tobias Unruh. "Characterization of lipid nanoparticles by differential scanning calorimetry, X-ray and neutron scattering." *Advanced drug delivery reviews* 59.6 (2007): 379-402.
9. York, P. (1992). Crystal engineering and particle design for the powder compaction process. *Drug Development and Industrial Pharmacy*, 18(6-7), 677-721.
10. Bhatnagar, Bakul, et al. "Protein/ice interaction: high-resolution synchrotron X-ray diffraction differentiates pharmaceutical proteins from lysozyme." *The Journal of Physical Chemistry B* 123.27 (2019): 5690-5699.
11. Nasiri-Tabrizi, Bahman, Abbas Fahami, and Reza Ebrahimi-Kahrizsangi. "A comparative study of hydroxyapatite nanostructures produced under different milling conditions and thermal treatment of bovine bone." *Journal of Industrial and Engineering Chemistry* 20.1 (2014): 245-258.