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**Der Pharma Chemica, 2013, 5(1):279-283**
*(http://derpharmachemica.com/archive.html)*

**ISSN 0975-413X**
**CODEN (USA): PCHHAX**

# Polymorphism in fexofenadine hydrochloride

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**ABSTRACT**

*Three polymorphic modifications of Fexofenadine hydrochloride designated as Form A1, Form B1 and Form C1 have been obtained by recrystallization in organic solvents under variable conditions. Different polymorphs of Fexofenadine hydrochloride were characterized by powder X-ray crystallography diffractometry (PXRD), differential scanning calorimetry (DSC), and thermo gravimetric analysis (TGA).*

**Keywords:** Fexofenadine hydrochloride, Crystal form, Polymorphism, PXRD

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## INTRODUCTION

Pharmaceutical solids can exist in different crystal forms, such as crystalline, amorphous, or glass, and also in solvated or hydrated states [1-3]. Polymorphism is the ability of any element or compound to crystallize as more than one distinct crystal species. Polymorphism is widely observed in pharmaceutical compounds and continues to be an important issue in drug development because of its impact on the physicochemical properties of drugs [4]. It is well recognized that polymorphism and solvate formation affect the various pharmaceutically important physicochemical properties, such as stability, solubility, dissolution rate, crystal habit (shape), tableting behavior [3, 5-7]. The presence of this phenomenon in pharmaceuticals is particularly common and a report lists over 500 examples of pharmaceuticals that exhibit polymorphism [8]. Changes in certain of these physicochemical properties may ultimately affect the bioavailability of the drug [9-10] which is also dependent upon other factors that govern the rate and extent of drug absorption. In this context, the Biopharmaceutics Classification System (BCS) provides a useful scientific framework for regulatory decisions regarding drug polymorphism [11]. For a drug whose rate and extent of absorption is limited by its dissolution, large differences in the solubilities of the various polymorphic forms are likely to affect bioavailability. In the case of a drug whose absorption is solubility-limited and thus cannot achieve the systemic exposure required for therapy, a more soluble form of the drug is desired to deliver the therapeutic dose [12].

Fexofenadine hydrochloride ((RS)-2-[4-[1-Hydroxy-4-[4-(hydroxy-diphenyl-methyl)-1-piperidyl]butyl]phenyl]-2-methyl-propanoic acid hydrochloride, $C_{32}H_{39}NO_4$.HCl) is an antihistamine drug used in the treatment of hay fever and similar allergy symptoms. It was developed as a successor of an alternative to Terfenadine an antihistamine that caused QT interval prolongation, potentially leading to cardiac arrhythmia. Fexofenadine hydrochloride, like other second- and third-generation antihistamines, does not readily cross the blood-brain barrier, and so causes less drowsiness than first-generation histamine-receptor antagonists. It works by being an antagonist to the $H_1$ receptor. It has been described as both a second-generation and third-generation antihistamine.

Fexofenadine hydrochloride is indicated for the relief from physical symptoms associated with seasonal allergic rhinitis and treatment of chronic urticaria. It is not a therapeutic drug and does not cure but rather prevents the aggravation of rhinitis and urticaria and reduces the severity of the symptoms associated with those conditions, providing much relief from repeated sneezing, runny nose, itchy eyes and general body fatigue.

## MATERIALS AND METHODS

### Materials

Fexofenadine hydrochloride was provided from Parth Laboratories Pvt. Ltd. Other chemicals and solvents were of analytical reagent or special grade.

### Preparation of polymorphic forms

#### Form A1

3 g of Fexofenadine hydrochloride were slurried in 20 mL of n-propanol. The mixture was stirred at room temperature for a slurry time of 24 hours with a magnetic stirrer. The mixture was filtered under vacuum, rinsed with n-propanol (10 mL), dried and analyzed by PXRD analysis and showed to be Form A1.

#### Form B1

3 g of Fexofenadine hydrochloride were slurried in 20 mL of ethanol. The mixture was stirred at room temperature for a slurry time of 16 hours with a magnetic stirrer. The mixture was filtered under vacuum, rinsed with ethanol (10 mL), dried and analyzed by PXRD analysis and showed to be Form B1.

#### Form C1

3 g of Fexofenadine hydrochloride were slurried in 20 mL of methanol. The mixture was stirred at 45°C temperature for a slurry time of 28 hours with a magnetic stirrer. The mixture was filtered under vacuum, rinsed with methanol (10 mL), dried and analyzed by PXRD analysis and showed to be Form C1.

### Methods

#### Powder X-ray diffraction

Powder X-ray diffraction (PXRD) patterns under ambient conditions were collected on Rigaku DMAX-IIIA diffractometer using graphite monochromatized CuKα radiation (λ=1.54178 Å). The measurement conditions were isothermal; target, Cu; voltage, 30kV, current, 10mA.

#### Thermal Analysis

The DSC thermogram was obtained using a Shimadzu DSC-50 instrument. The temperature range of scans was 30-350°C at a rate of 10°C/min. The weight of the sample was 2-5 mg. The sample was purged with nitrogen gas at a flow rate of 40 mL/min. Standard 40 µl aluminum crucibles having lids with three small holes were used. The TGA thermogram for Fexofenadine hydrochloride form was performed on TGA-50 instrument (Shimadzu) using alumina pan and a sample weight 7-15 mg.

## RESULTS AND DISCUSSION

X-ray powder diffraction patterns of three Fexofenadine hydrochloride polymorphs are presented in Fig. 2. DSC curve of Fexofenadine hydrochloride Form A1 is illustrated in Fig. 3. DSC curves of Fexofenadine hydrochloride Form B1 and Form C1 are illustrated in Fig. 4. TGA curves of Fexofenadine hydrochloride Form A1, Form B1 and Form C1 are illustrated in Fig. 5. The DSC, TGA and PXRD results confirmed the existence of three crystal forms of Fexofenadine hydrochloride.

Henton *et al.* [13] described four polymorphic forms of Fexofenadine hydrochloride designated as Form I (anhydrous), Form II (hydrate), Form III (anhydrous) and Form IV (hydrate). Kumar *et al.* [14] described amorphous Fexofenadine hydrochloride. Kirsch [15] described anhydrous Form A of Fexofenadine hydrochloride. Dolitzky *et al.* [16] described ten polymorphic forms of Fexofenadine hydrochloride designated as Form V, Form VI, Form VIII, Form IX (anhydrous or MTBE/Cyclohexane solvate), Form X, Form XI, Form XII, Form XIII, Form XIV (Ethyl acetate solvate) and Form XV (Ethyl acetate solvate). Milla [17] described Pentanone solvate of Fexofenadine hydrochloride. Krochmal *et al.* [18] described hydrate form of Fexofenadine hydrochloride designated as Form XVI. Kor *et al.* [19] described three polymorphic forms of Fexofenadine hydrochloride designated as Form XIX, Form XX and Form XXI. Castaldi *et al.* [20] described two polymorphic forms of Fexofenadine hydrochloride designated as Form B (monohydrate) and Form C (Acetonitrile monosolvate). Suri *et al.* [21] described Form IXX of Fexofenadine hydrochloride. Baratella [22] described Form Ψ of Fexofenadine hydrochloride.

**Fig. 1 Structure of Fexofenadine hydrochloride**

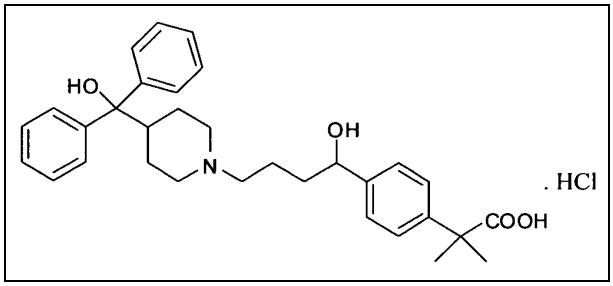



**Fig. 2 X-ray powder diffraction patterns of three Fexofenadine hydrochloride forms**

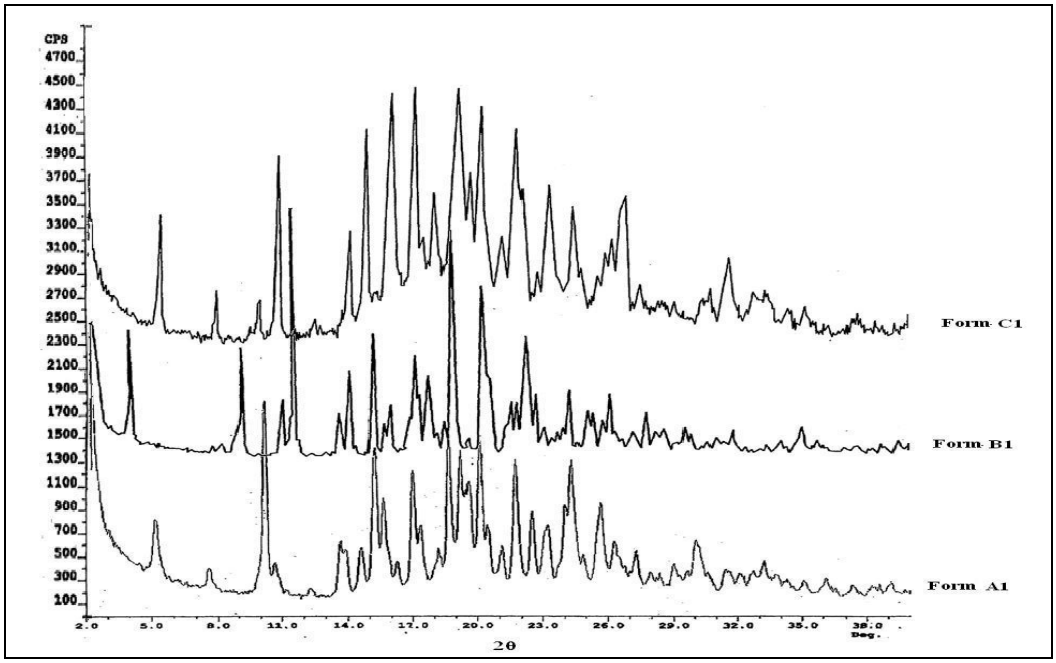



**Fig. 3 DSC curve of Fexofenadine hydrochloride A1 form**

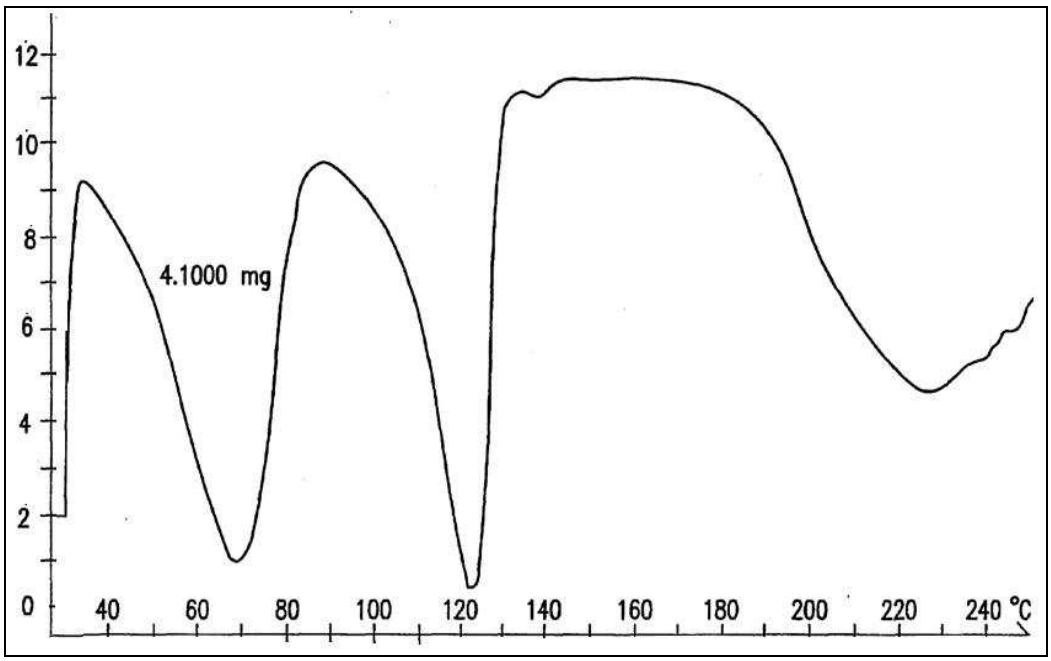


**Fig. 4 DSC curves of Fexofenadine hydrochloride B1 and C1 forms**

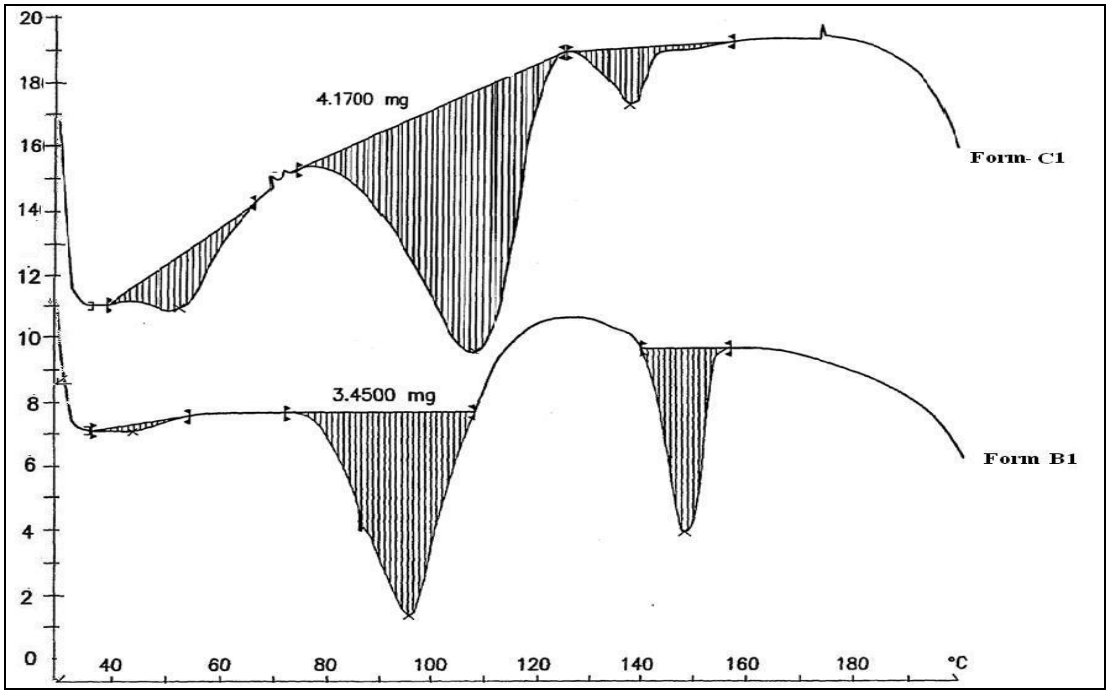
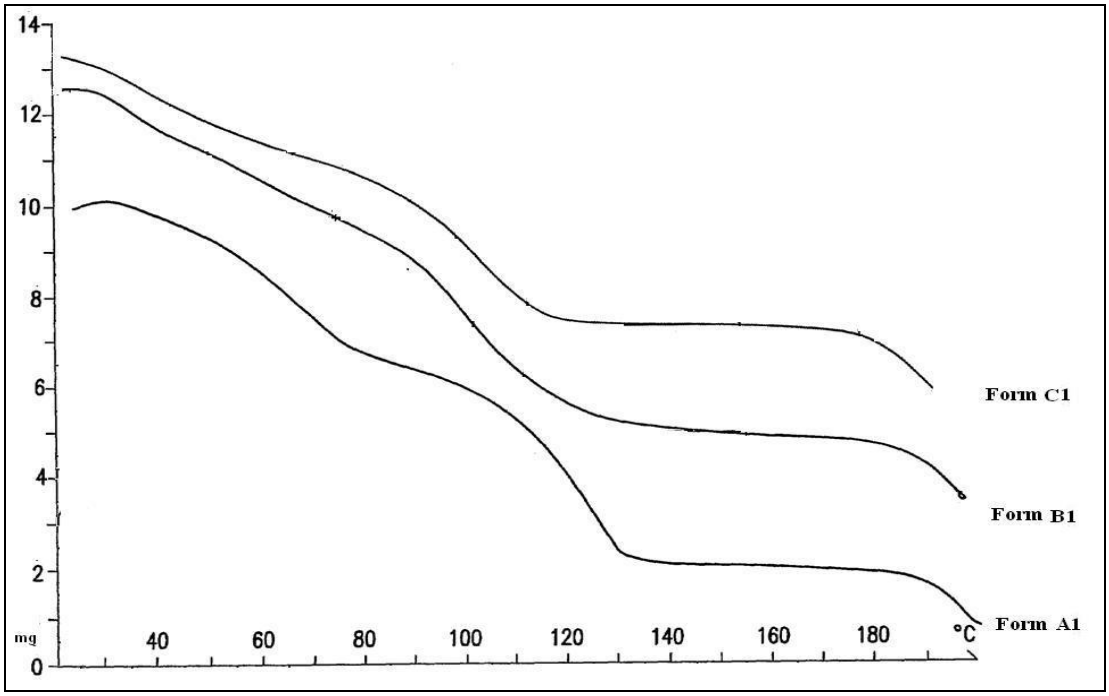



**Fig. 5 TGA curves of three Fexofenadine hydrochloride forms**




## CONCLUSION

Three crystal forms of Fexofenadine hydrochloride were prepared by recrystallization from different solvents. The crystal forms were characterized by DSC, PXRD and TGA. X-ray diffraction patterns of three Fexofenadine hydrochloride forms are different from those reported in literature [13-22].

**Acknowledgement**
The authors would like to thank Head, Department of Chemistry and Physics, Saurashtra University for providing infrastructure and other facilities. The authors would also like to thank Parth Laboratories Pvt. Ltd. for providing Fexofenadine hydrochloride.

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