**ISSN: 0976-4607**
**Research Article**

International Journal of Innovative Pharmaceutical Research

Journal homepage: www.ijipr.com

# Preparation and Characterization of Novel Co-Crystal Forms of Fexofenadine

**P. Mounika[1]*, S.Vijaya Raj[1], G. Divya[1], A. Gowramma[2] and G.Vijayamma[3]**
[1]Department of Pharmaceutical Analysis, Sree Vidyanikethan College of Pharmacy, A.Rangampet, Tirupati, Andhra Pradesh, India.
[2]Department of pharmaceutics, Sri Padmavathi School of Pharmacy, Tiruchanoor, Tirupati, Andhra Pradesh, India.
[3]Department of pharmaceutical Analysis, P. Ramireddy memorial College of Pharmacy, Kadapa, Andhra Pradesh, India.

**ABSTRACT**

By the improving physicochemical properties of Active Pharmaceutical Ingredient (API) such as solubility, stability and bioavailability Pharmaceutical co-crystallization techniques has gained a lot of attention. A pharmaceutical co-crystal is a single crystalline solid that incorporates two neutral molecules, one being an active pharmaceutical ingredient (API) and the other a co-crystal former. The present investigation involves formulation and solubility enhancement of a co-crystal based solid dosage form consisting of a stoichiometric amount of parent drug Fexofenadine with a pharmaceutically acceptable co-former Tartaric acid. Firstly co-crystals are prepared through Solvent evaporation method by taking Fexofenadine and Tartaric acid in 1:1 ratio. Co-crystal formation is confirmed by infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), Microscopic studies. The supramolecular interaction of fexofenadine with dicarboxylic acids resulted in formation of hydrogen bonding between them. Prepared Co-crystals are subjected to Preliminary pharmaceutical characterization such as solubility, Drug content, percentage yield and Invitro dissolution studies. DSC, SEM and FTIR analysis confirm the formation of molecular complex. When compared to the formulation of Fexofenadine the formed cocrystal has shown max drug release of 86.9% with 0.01 N HCL as a dissolution medium. From the pharmaceutical characterization, prepared molecular complex has shown increased solubility and increased drug release profile.

**Keywords:** Co-Crystallization, Fexofenadine, Tartaric acid, FT-IR, DSC.

## INTRODUCTION

To attain the desired therapeutic action of the drug it should have good solubility among the body fluids as well as good stability in the external environment. Even though the pharmaceuticals have good solubility in their amorphous forms lack stability. Prior to solubility, stability creates a challenging task to the developers in formulating the products throughout their shelf life.

The process of crystallization had resolved the problem of stability as well as solubility which gave strength to the pharmaceutical industry. Co-crystallization is also referred as molecular complexing. Co-crystals are defined as multiple component structures whose components interact by non-covalent interactions such as hydrogen bonding or other weak intermolecular interactions rather than by ion pairing (Fleischman S.G et al, 2003, McMahon J.A et al, 2005, Sharma C.V.K *et al*., 2006). A pharmaceutical co-crystal is a single crystalline solid that incorporates two neutral molecules, one being an API and the other a co-crystal former (Rodríguez-Hornedo N *et al*., 2007). Co-crystal former may be an excipient or another drug (Remenar JF *et al*., 2003). Currently co-crystal approach is a method of great interest for the pharmaceutical industry. Apart from offering potential improvements in solubility, dissolution rate, bioavailability and physical stability, pharmaceutical co-crystals can enhance other essential properties of the APIs such as flowability, chemical stability, compressibility and hygroscopicity (Schultheiss N *et al*., 2009, Peterson ML *et al*., 2006).

The crystallization of the drug products is attained by several methods amongst where the technique of solvent evaporation is majorly used. The approach of

***Corrosponding author**

**P. Mounika**
**Email id:** mounikampharma@gmail.com

crystallization alters the physico chemical properties of the drug product without altering its original pharmacological response. Hence this technique is well chosen in the current pharmaceutical (physico chemically) modification of drugs.

Fexofenadine is an anti-histaminic agent that acts as a second-generation selectively peripheral H1-blocker and used in the treatment of rashes, hay fever, sneezing, rhinorrhea, utricaria, allergic rhinitis and hypersensitivity reactions with manifestations such as angioedema, dyspnea, flushing and systemic anaphyylaxis (B. Rashmika *et al*., 2013). Fexofenadine being the class II drug according to the BCS classification having low solubility and high permeability, the rate limiting steps in attaining desired bioavailability. Hence the co-crystals of Fexofenadine were prepared using Tartaricacid as a co-former (1:1) by solvent evaporation.

## MATERIALS AND METHODS

### Materials

Fexofenadine (Matrix Pvt. Ltd., Hyderabad), Tartaric acid (SD fine chem., Mumbai), Hydrochloric acid (SDfine chem., Mumbai).

### Synthesis of Co-Crystals

### Solvent evaporation technique

This technique is the common way to synthesize cocrystals. In this method cocrystal components or cocrystal formers are taken in stoichiometric ratio and solubilise in a common solvent. The resultant solution is allowed to evaporate slowly. This technique works on the principle that, when different molecules of complimentary functional groups afford hydrogen bonds that are more favorable than each of the individual molecular components. In this case, the cocrystal is likely to be thermodynamically favored (Jayasankar A, Somwangthanaroj A *et al*., 2006).

### Synthesis of Cocrystal forms of Fexofenadine - Tartaric acid (1:1)

The accurately weighed drug and co-former, 501mg of fexofenadine and 138mg of Tartaric acid (1:1 molar ratio) were dissolved in 10 ml of water on slow heating and left for slow evaporation. The fine crystals were obtained after evaporation which were collected into a tight container and stored in desiccators till further use.

### Characterization of Prepared Co-Crystals

FT-IR, DSC and microscopic studies have been performed for the co crystals by the afore mentioned procedure.

### a. FT-IR studies

IR spectroscopy was conducted using a FTIR Spectrophotometer (Thermo-IR 200) and Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. The spectrum of Fexofenadine, L(+) Tartaric acid and prepared co-crystals were recorded in the wavelength region of 4000–400 cm−1 (Callear S.K, 2008).

### b. Microscopic studies studies

The surface characteristics of Fexofenadine, Tartaric acid and cocrystal were studied by ZEISS Electron Microscope, EVO MA15. The specimens were scanned with an electron beam of acceleration potential of 20 kV and the images were collected as secondary electron mode.

### c. DSC studies

Thermal analysis of Fexofenadine, Tartaric acid, and cocrystal were recorded on a DSC (NETZSCH DSC 204). The temperature axis and cell constant of DSC were previously calibrated with indium. A heating rate of 100C/min was employed with nitrogen pursing. Powder samples (15-30 mg) was weighed into an aluminum pan and analyzed as sealed with pin holes and an empty aluminum pan was used as reference (Wenger M and Bernstein J, 2008).

### Evaluation of Cocrystals

### Dissolution studies

The dissolution of cocrystals were studied using USP Type II dissolution apparatus containing 900ml 0.01N Hcl maintained at 37±0.5 $^0$C and stirred at 75 rpm. Dissolution studies have been performed for the formulation of Fexofenadine, and cocrystals fexofenadine: Tartaric acid (1:1) ratio in 0.01N HCl. 5 mL of sample was withdrawn after suitable time interval and replaced each time with 5mL fresh medium. The solutions were immediately filtered through 0.45 mm membrane filter, diluted and the concentration of drug was determined with the help of UV spectrophotometer (Schimadzu) at wavelength of 259nm. Percentage of drug dissolved was calculated by plotting time on X- axis against % cumulative drug release on Y-axis (Sonia dhiman *et al*., 2012).

### Saturation Solubility studies

Solubility measurements were performed according to the method of Higuchi and Connors (1965). Drug solubility studies were performed by adding excess amounts of Fexofenadine and prepared co-crystals to water and 0.01 N HCL buffer in separate vials. The vials containing drug-hydrophilic polymer carrier mixtures were shaken at 37.0±0.5 ° C for 48 h in water bath shaker (Remi Pvt Ltd, Mumbai). After 48 hr, samples were filtered through a 0.45-µm filter paper and analyzed in UV spectrophotometer at wavelength of 259nm. Solubility studies were performed in triplicate (n=3) (Sammour et al., 2006).

### Percentage practical yields

Percentage practical yield of prepared Cocrystals was calculated to know about percent yield or efficiency of method. Cocrystals were collected and weighed to determine practical yield (PY) from the following equation.

**Percentage of practical yield** = $\frac{\text{practical yield}}{\text{theoritical yield}}$ x 100

**Drug Content**

From each batch of prepared Cocrystals three samples of 10 mg were taken and analyzed for drug content. 10 mg of each sample was weighed and transferred in 100 ml standard flasks and volume was made up to 100 ml with Hcl buffer. The solutions were filtered through a 0.45µ membrane filter and diluted. One ml from above the solution was transferred into a 10 ml standard flasks and volume made up to 10 ml with HCl buffer. Absorbance of the solutions was measured at 284 nm.

## RESULTS AND DISCUSSION

**FTIR studies**

FTIR spectrum of Fexofenadine showed characteristic peaks of NH stretch at 3368.12 $cm^{-1}$, Aromatic C-H stretch at 2968.81 $cm^{-1}$, C=O stretch at 1716.85 $cm^{-1}$, O-H stretch at 3063.33 $cm^{-1}$ and Aromatic C=C stretch at 1488.72 $cm^{-1}$. FTIR spectrum of tartaric acid showed a characteristic peak OH at 3322.23 $cm^{-1}$ and C=O peak at 1735.11 cm $^{-1}$. FTIR spectrum of Fexofenadine Co-crystals showed shift in characteristic peaks of Fexofenadine. NH stretch at 3368.12 $cm^{-1}$ Shifted to 3319.42 $cm^{-1}$, Aromatic C-H stretch at 2968.81 $cm^{-1}$ Shifted to 3000.37 $cm^{-1}$, C=O stretch at 1716.85 $cm^{-1}$ Shifted to1690.78 $cm^{-1}$ , O-H stretch at 3063.33 $cm^{-1}$ Shifted to 3000.37 $cm^{-1}$ and Aromatic C=C stretch at 1488.72 $cm^{-1}$ Shifted to 1447.04 $cm^{-1}$. The shift in characteristic peaks of Fexofenadine and appearance of a new peak of OH bonding at 3226.8 $cm^{-1}$ represents formation of Co-crystals.

The possible interaction between the drug and the L(+)tartaric acid were studied by IR spectroscopy. Fexofenadine generally occurs in salt form i.e, Fexofenadine HCl. Fexofenadine has nitrogen containing pyridyl ring which has lone pair of electrons. This lone pair of electrons reacts with that of "H" in HCl. As a result of this,there will be NH bonding. So NH stretching is seen in IR spectrum of fexofenadine. This NH is mainly responsible for interaction of fexofenadine with C=O group of one COOH of tartaric acid. The heterosynthon can be formed when NH of fexofenadine interacts with C=O group of one COOH of tartaric acid. Homosynthon can be formed when COOH of tartaric acid reacts with COOH of fexofenadine.

**Differential scanning calorimetry (DSC)**

DSC experiments were carried out to study the thermal behavior of the prepared crystal form in relation to the individual components. DSC thermal data are shown in figure no.60. DSC study of fexofenadine and L(+) tartaric acid shows endothermic peak at 188.55 $^0$C and 179.62 $^0$C while DSC study of prepared cocrystal form of Fexofenadine and L(+)tartaric acid (1:1) shows sharp endothermic peak at134.64$^0$C, the sharp endothermic values of prepared crystal form and the individual components agreed with the measured melting range in the melting point determination. The thermal profile of crystal form was distinct, with a different melting transition from that seen with either of the individual components. This indicates the formation of novel molecular complex.

**Microscopic studies**

Microscopic studies of pure drug, Tartaric acid and crystal form are shown in the figure.3. They represent rod like, triangular and plate like crystals respectively.

**Release kinetics**

The data obtained from invitro studies is subjected to zero order, first order, Higuchi model, krosmeyer model, hixsoncrowell model.

**Percentage practical yield**

The percentage of practical yield of the solvent evaporation technique for preparation of Co-crystals of Fexofenadine using Tartaric acid as coformer was found to be 78.64%.

**Saturation Solubility studies**

The saturation solubility studies of pure drug and prepared Co-crystals were performed in 0.01 N HCL and water. The solubilty of Co-crystals in water is 11 folds more than the pure drug and solubilty of Co-crystals in 0.01 N HCL is 2.47 folds more than the pure drug.

**Drug content**

The drug content of the prepared Co-crystals was found to be 92.78%.

**Evaluation of Cocrystals**

**Dissolution studies: Dissolution data in 0.01 N HCl**

**Table.1 Dissolution data in in 0.01 N HCl**

| S.No | Time (min) | % Drug Release | |
|---|---|---|---|
| | | Fexofenadine tablets | Fexofenadine:tartaric acid 1:1 |
| 1 | 0 | 12.76 | 26.66 |
| 2 | 10 | 29.45 | 36.05 |
| 3 | 20 | 29.82 | 49.87 |
| 4 | 30 | 29.82 | 59.75 |
| 5 | 40 | 31.73 | 66.65 |
| 6 | 50 | 34.5 | 73.07 |
| 7 | 60 | 37.41 | 86.9 |

**Table.2 Release parameters of drug and prepared cocrystal in 0.01 N HCL**

| Release kinetics | | Zero order kinetics | First order kinetics | Higuchi model | Krosmeyer model | Hixson crowell model |
|---|---|---|---|---|---|---|
| Drug | $R^2$ | 0.7078 | 0.1886 | 0.8915 | 0.7716 | **0.9661** |
| | m | 3.07 | 5.6496 | 8.8552 | 0.4869 | -0.0564 |
| | c | 20.146 | 44.754 | 15.653 | 1.1953 | 4.6007 |
| Crystal form | $R^2$ | 0.9888 | 0.0052 | 0.9267 | 0.9904 | 0.9661 |
| | m | 9.6979 | -0.8175 | 24.13 | 0.585 | -0.0564 |
| | c | 27.899 | 43.588 | 19.655 | 1.4122 | 4.6007 |

**Table.3 Solubility studies of domperidone cocrystals**

| S.No | Formulation | Solubility(mg/ml) | |
|---|---|---|---|
| | | water | 0.01 N HCL buffer |
| 1 | Drug | 0.026 | 0.143 |
| 2 | Co-crystal | 0.286 | 0.354 |

**Figure.1 FTIR spectrums of (A) Fexofenadine, (B) L(+)tartaric acid and (C) Co-crystal**

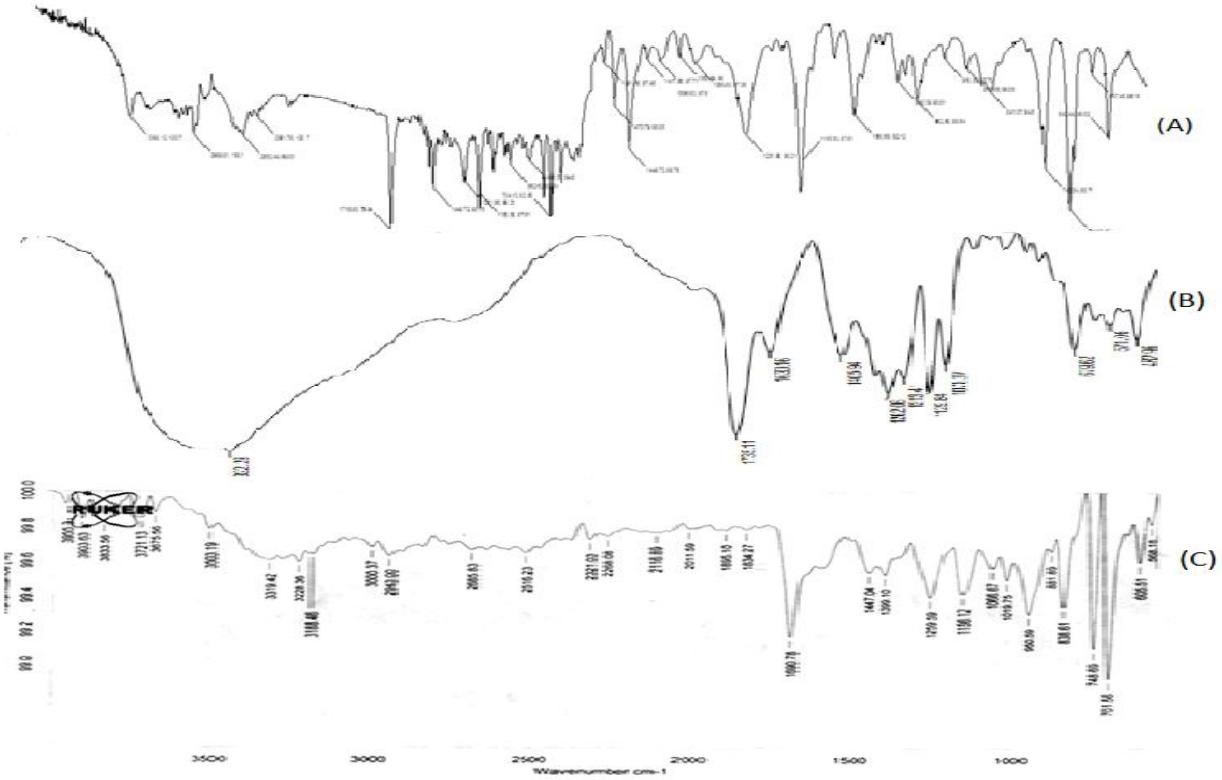



**Figure.2 DSC thermo grams of (A) Fexofenadine, (B) L(+)tartaric acid and (C) Cocrystal**

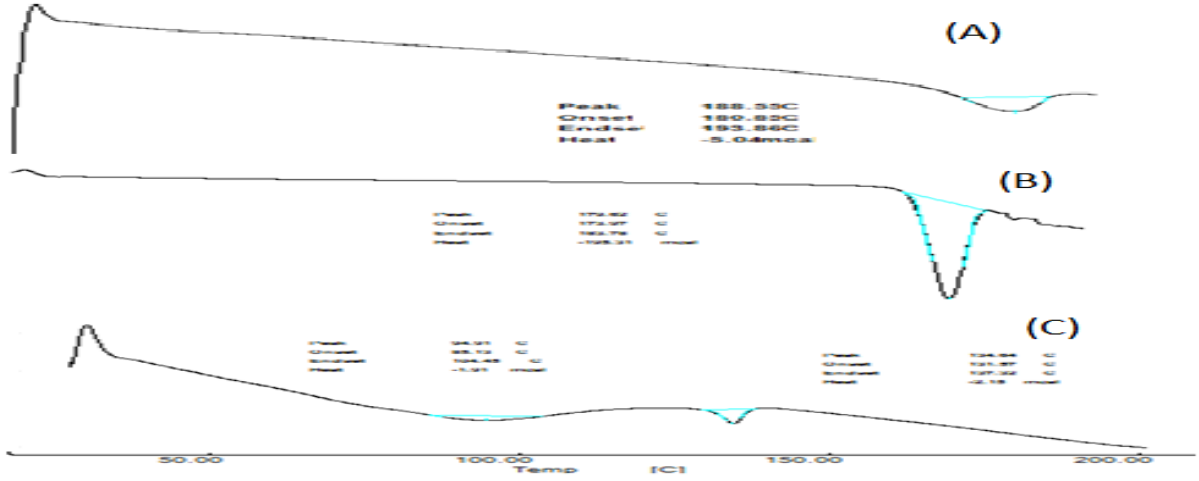
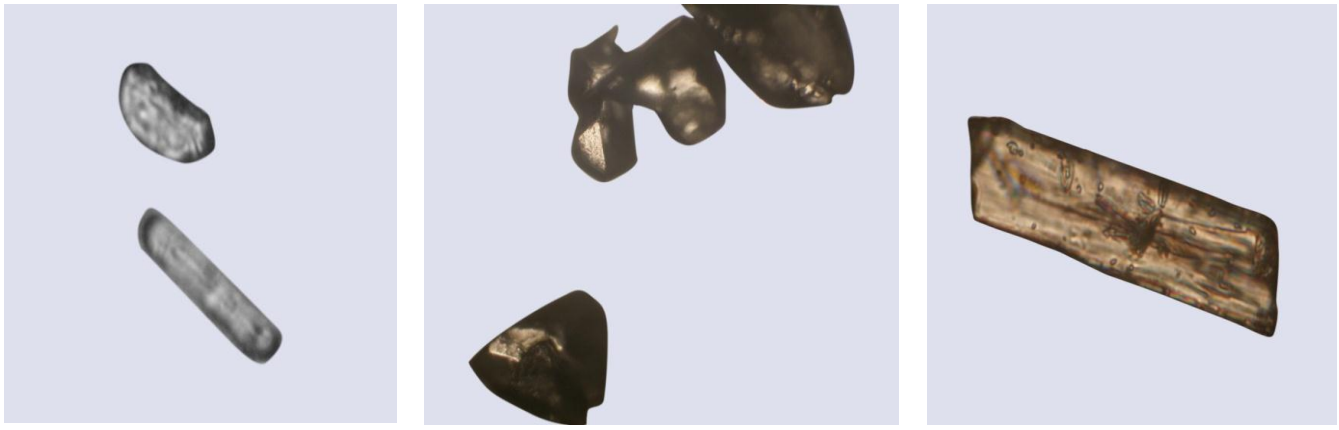
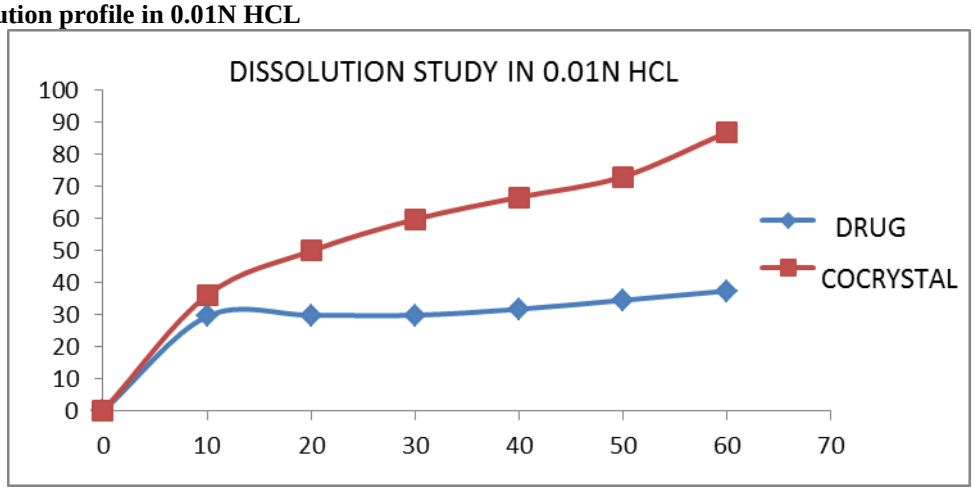


**Figure.3 Microscopic images of (A) Fexofenadine (B) Tartaric acid (C) Cocrystal form of fexofenadine and tartaric acid**



(A) (B) (C)

**Figure.4 Dissolution profile in 0.01N HCL**




## CONCLUSION

The core point to proceed with this work is to improve the solubility of Fexofinadine. Among the various methods of improving solubility, the co-crystal formation by solvent evaporation technique has proven to be advantageous due to its simple mode of preparation, here the stability as well as the solubility of the drug is improved. A novel co-crystals of Fexofenadine and Tartaric acid of (1:1) ratio was prepared by Co-crystallisation technique and has shown a maximum drug release when compared to the formulation. Finally it was concluded that the solubility of Fexofenadine was increased by using solvent evaporation method.

## REFERENCES

Callear S.K. Preparation, characterization and structural analysis of salts and co-crystals of organic compounds. University of Southampton, School of Chemistry, PhD Thesis, 2008;253.

Fleischman S.G, Kuduva S.S, McMahon J.A, Moulton B, Walsh R.B, Rodriguez-Hornedo N and Zaworotko M.J. Crystal Engineering of the Composition of Pharmaceutical Phases:Multiple- Component Crystalline Solids Involving Carbamazepine. *Cryst. Growth Des.* 2003;3:909.

Jayasankar A, Somwangthanaroj A et al. Cocrystal formation during cogrinding and storage is mediated by amorphous phase. *Pharmaceutical Research*. 2006;23:2381-2392.

McMahon J.A, Bis J.A, Vishweshwar P, Shattock T.R, McLaughlin O.L and Zaworotko M.J. Crystal engineering of the composition of pharmaceutical phases. Primary amide supramolecular heterosynthons and their role in the design of pharmaceutical cocrystals. *Zeit. Fur Krist.* 2005;220:340-350.

Peterson ML, Hickey MB, Zaworotko MJ, Almarsson O. Expanding the scope of crystal form evaluation in pharmaceutical science. *J Pharm Pharmaceut Sci*. 2006;9(3):317-326.

Rashmika. B. et.al., Formulation development and *In Vivo* evaluation of fexofenadine HCl solidd dispersions by spray drying technique. *Der Pharmacia Lettre*. 2013;5(6):73-82.

Remenar JF, Morissette SL, Peterson ML, Moulton B, MacPhee JM, Guzmán H, Almarsson O, Crystal engineering of novel co-crystals of a triazole drug with 1,4-dicarboxylic acids. *J Am Chem Soc*. 2003;125:8456-8457.

Rodríguez-Hornedo N, Nehm SJ, Jayasankar A. Cocrystals: design, properties and formation mechanisms, In Encyclopedia of Pharmaceutical Technology, 3rd ed, Taylor & Francis, London, 2007: 615-635.

Sammour O., Hammad M., Megrab N., Zidan A. Formulation and optimization of mouth dissolve tablets containing Rofecoxib solid dispersion. AAPS PharmSciTech. 2006;7(2):E 55.

Schultheiss N, Newman A. Pharmaceutical co-crystals and their physicochemical properties. *Cryst Growth Des*, 2009;9:2950–2967.

Sharma C.V.K and Zaworotko M.J. X-Ray crystal structure of C6H3 (CO2H)3-1,3,5·1.5(4,4′ bipy): a 'super trimesic acid' chicken-wire grid. *Chem. Commun*. 2006;2655-2656.

Sonia dhiman, Thakur gurjeet singh. Design and optimization of floating matrix tablets of famotidine by central composite design. *Asian Journal of Pharmaceutical and Clinical Research.* 2012;5(1):45-49.

Wenger M and Bernstein J. An alternate crystal form of gabapentin: A cocrystal with oxalic acid. *Cryst Growth Des*. 2008;8:1595–1598.