

SOLID DISPERSION TECHNIQUE TO ENHANCE THE SOLUBILITY AND DISSOLUTION OF FEBUXOSTAT AN BCS CLASS II DRUG

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ABSTRACT

Objective: The present study was aimed to enhance the solubility of poorly water-soluble drug (BCS Class II) Febuxostat using water-soluble polymers.

Methods: Pre-formulation studies like drug excipient compatibility studies by Fourier-transform infrared spectroscopy, Differential scanning calorimetry and determination of saturation solubility of drug individually in various media like distilled water and pH 7.4 phosphate buffer. Solid dispersions of Febuxostat was prepared using Polyethylene glycol (PEG 6000) (fusion method) and Polyvinyl pyrrolidone (PVP K30) (solvent evaporation method) in various ratios like 1:1, 1:2, 1:3 and 1:4 separately. The formulated solid dispersions were evaluated for percentage yield, drug content and *in vitro* dissolution studies.

Results: From the results of pre-formulation studies it was revealed that there was no interaction between drug and excipients and the pure drug was poorly soluble in water. The percentage yield of all formulations was in the range of 54-78 %, and drug content was in the range of 43-78 mg. The solid dispersion containing polyvinylpyrrolidone K 30 in 1:4 ratio showed the highest amount of drug release at the end of 30 min than other formulations.

Conclusion: Finally it was concluded that solid dispersion prepared with PVP K-30 in 1:4 ratio by solvent evaporation method was more soluble than by fusion method.

Keywords: Febuxostat, Solubility, PEG 6000

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INTRODUCTION

The solubility/dissolution behavior of a drug is the key factor influencing its oral bioavailability, being the rate-limiting step for absorption of drugs from the gastrointestinal tract. Consequently poor solubility results in low bioavailability increase in the dose, large inter- and intra-subject variation and large variations in plasma drug concentrations under fed versus fasted conditions [1, 2].

Dissolution and solubility are two important parameters which alter oral bioavailability of any drug; thus efforts should be done to improve the solubility and dissolution rate is essential. Characteristics of the drugs can be altered by converting them into salt forms, size reduction, and by adding surfactants [3].

Based on the solubility of the drug and its gastrointestinal permeability, they become the fundamental parameters for rate controlling and extent of drug absorption inside the body. The Biopharmaceutics Classification System correlates the *in vitro* drug dissolution and *in vivo* bioavailability.

To determine the bioavailability of fast dissolving drugs with high solubility, a simple one point dissolution test and for drugs dissolving slowly, a multiple point dissolution test should be performed which includes low pH, physiological pH, and surfactants so that the *in vitro* conditions should be a mirror as that of the *in vivo* process [4, 5].

Solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous [6, 7].

The present study was aimed to enhance the solubility of poorly water-soluble drug (BCS Class II) Febuxostat using water-soluble polymers PEG 6000 and PVP K30.

MATERIALS AND METHODS

Febuxostat gift sample was obtained from Ranbaxy, Mumbai, Polyethylene glycol 6000 from Borepharm Co., Ltd, Povidone from

Sigma-Aldrich, Ethanol from Changshu Hongsheng fine chemicals Co., Ltd., Potassium dihydrogen phosphate from Merck Specialties Private Limited, Sodium hydroxide from Lobal Chemie Laboratory Reagents and Fine Chemicals.

Preparation of PH 7.4 phosphate buffer

Potassium dihydrogen phosphate, 0.2N

About 28.2 g of potassium dihydrogen phosphate was dissolved in small amount of water and then diluted to 1000 ml with water.

Sodium hydroxide, 0.2N

About 8 g of sodium hydroxide was dissolved in small amount of water and then diluted to 1000 ml with water.

pH 7.4 phosphate buffer

About 50 ml of 0.2N potassium dihydrogen phosphate was taken in a 200 ml volumetric flask. To this 39.1 ml of 0.2N sodium hydroxide solution was added and diluted to 200 ml with water.

Determination of λ_{MAX} for febuxostat in PH 7.4 phosphate buffer

About 100 mg of Febuxostat was accurately weighed into 100 ml volumetric flask. Volume is made up to 100 ml using pH 7.4 phosphate buffer after dissolving Febuxostat completely. 20 ml was pipetted out from the above solution and diluted to 100 ml using pH 7.4 phosphate buffer. The solution was diluted suitably and scanned in the range of 200-400 nm using UV Spectrophotometer with pH 7.4 phosphate buffer as blank. From the spectrum obtained, the λ_{max} for Febuxostat was found to be 315 nm in pH 7.4 phosphate buffer [8].

Standard graph for febuxostat in PH 7.4 phosphate buffer

About 100 mg of Febuxostat was accurately weighed into 100 ml volumetric flask. Volume is made up to 100 ml using pH 7.4 phosphate buffer after dissolving Febuxostat completely. This is the primary stock solution, and from this primary stock solution, 20 ml

was withdrawn and made up to 100 ml with pH 7.4 phosphate buffer. This is called secondary stock solution. From the above solution, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 ml was withdrawn and made up to 10 ml with pH 7.4 phosphate buffer separately to produce 2 to 20 µg/ml concentrations respectively. Using UV spectrophotometer the absorbances of these diluted solutions were measured at λmax

of 315 nm with pH 7.4 phosphate buffer as blank. Standard graph of the febuxostat was plotted with concentration (µg/ml) in x-axis and absorbance at 315 nm in y-axis is shown in.1. The concentrations and its absorbances were subjected to linear regression analysis, and the regression equation was found to be $y = 0.044x - 0.058$, and correlation coefficient (r²) was found to be 0.990

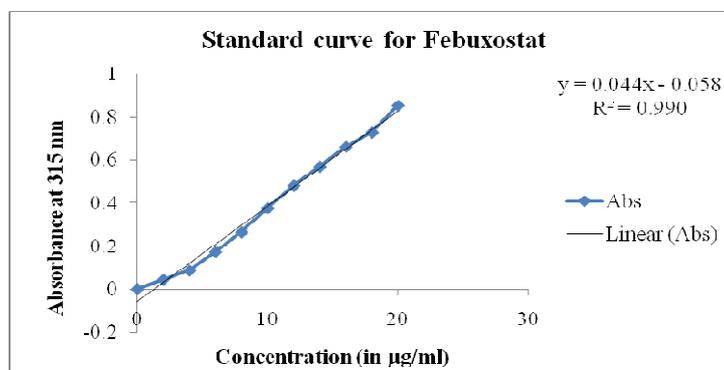


Fig. 1: Standard curve of febuxostat in pH 7.4 phosphate buffer

Pre-formulation studies

Drug-excipient compatibility studies

FTIR study

For all the formulations and Febuxostat, the pellets have been prepared using potassium bromide for FT-IR study. The pellets were subjected to FT-IR instrument 'Perkin Elmer FTIR spectrometer, spectrum 1000 Germany' for the collection of IR spectra which are illustrated in fig. 2 to 4 [9].

Differential scanning calorimeter (DSC) studies

Differential scanning calorimetry was done by using Differential scanning calorimeter 'PerkinElmer' to obtain the thermograms. Sample after weighing accurately were placed in an aluminum pan and another

empty aluminium pan was used as the reference. The scanning was done under nitrogen flow at a scanning rate 10 °C/min in range of 30-450 °C. Thermograms were obtained for pure drug, Febuxostat, Polyethylene glycol (PEG) 6000 and Polyvinylpyrrolidone (PVP) K 30 alone and also for combinations of the pure drug with the polymer in 1:1 ratio individually. The results are shown in fig. 5 to 8.

Determination of saturation solubility

Using the agitation method, the Solubility study was performed, and saturated solution of Febuxostat was prepared using distilled water and pH 7.4 phosphate buffer and it was stirred for 24 h. The solution filtered through whatmann filter paper 0.45 µm after centrifuging for 15 min over 10,000 rpm. The concentration of Febuxostat was determined using UV-visible spectrophotometer against respective solvent as blank at λmax of 315 nm. The results are shown in table 1.

Table 1: Saturation solubility of febuxostat in various medias

Name of the media	Saturation solubility of drug (in mg/ml)
Distilled water	0.84
pH 7.4 phosphate buffer	1.56

Development of solid dispersion

By fusion method

The solid dispersion of Febuxostat and PEG 6000 prepared in four different weight ratios (1:1, 1:2, 1:3 and 1:4) and denoted as FF1,

FF2, FF3 and FF4, respectively. With constant stirring Febuxostat was added to molten PEG 6000 and resulting homogenous dispersion was allowed to solidify. The solid dispersion thus formed was ground in the mortar and sieved to produce uniform particle size dispersion. Formulation codes are shown in table 2.

Table 2: Formula for the preparation of solid dispersion of febuxostat with different polymers

Formulation code	Formulation	Carrier	Drug: carrier	Method
FF1			1:1	
FF2	Solid Dispersion	PEG 6000	1:2	Fusion method
FF3			1:3	
FF4			1:4	
FF5			1:1	
FF6	Solid Dispersion	PVP K 30	1:2	Solvent evaporation
FF7			1:3	
FF8			1:4	

By solvent evaporation method

Solid dispersion of Febuxostat and PVP K-30 were prepared in four different weight ratios (1:1, 1:2, 1:3 and 1:4) and denoted as FF5, FF6, FF7 and FF8, respectively. The required quantity of PVP K-30 was dissolved in ethanol and to this Febuxostat was added. The

resulting solution was then homogenized thoroughly and evaporated the solvent. Complete removal of solvent was achieved by drying the mass obtained in the oven at 40 °C for 24 h.

The produced. Solid dispersion was then ground, sieved and kept for further analysis. Formulation codes are shown in table 2.

Characterization of solid dispersion

Determination of percentage yield

Percentage yield was calculated for each batches of solid dispersion with respect to theoretical yield and practical yield. The results are shown in table 3.

$$\text{Percentage yield} = \left(\frac{\text{Practical yield}}{\text{Theoretical yield}} \right) \times 100$$

Estimation of drug content in solid dispersion

Sample containing 50 mg of prepared solid dispersion was accurately weighed and dissolved in freshly phosphate buffer pH 7.4 in a 100 ml volumetric flask. The volume was made up to 100 ml with phosphate buffer pH 7.4. The absorbance of the resulting solution was measured at 315 nm for Febuxostat, against blank (phosphate buffer pH 7.4) using UV spectrophotometer. The results are shown in table 3.

In vitro dissolution rate studies on solid dispersions

The *In vitro* dissolution for the prepared solid dispersions was performed using Labindia Disso 2000 dissolution test apparatus.

Solid dispersions equivalent to 100 mg of Febuxostat were filled in empty hard gelatin capsules were placed in 900 ml of pH 7.4 phosphate buffer as dissolution medium. The speed was maintained at 50 rpm using the paddle for 30 min. The temperature of the dissolution medium was maintained constant at 37±0.5 °C throughout the study. Samples of about 10 ml were pipette out at regular time intervals at 10, 20 and 30 min. The sink condition was maintained by replacing with an equal volume of fresh dissolution medium. The withdrawn aliquots were filtered through whatmann filter paper 0.45 µ, suitably diluted and assayed for Febuxostat at 315 nm using UV spectrophotometer. The dissolution experiments were conducted in triplicate. The results are shown in fig. 9 [10].

RESULTS AND DISCUSSION

Pre-formulation studies

Drug-excipient compatibility studies (FTIR)

The FTIR studies were shown in fig. 2 to 4. From the results of pre-formulation studies, it was revealed that there no chemical incompatibility between drug and excipients from FTIR studies.

Agilent Resolutions Pro

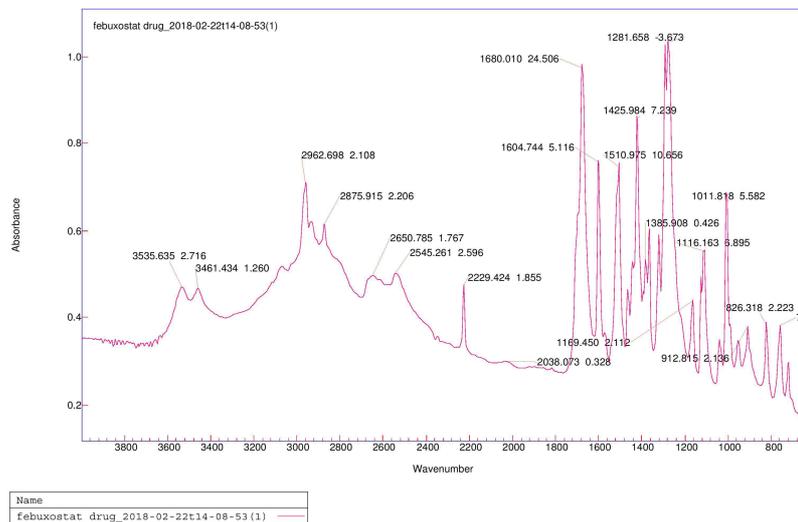


Fig. 2: FTIR for febuxostat

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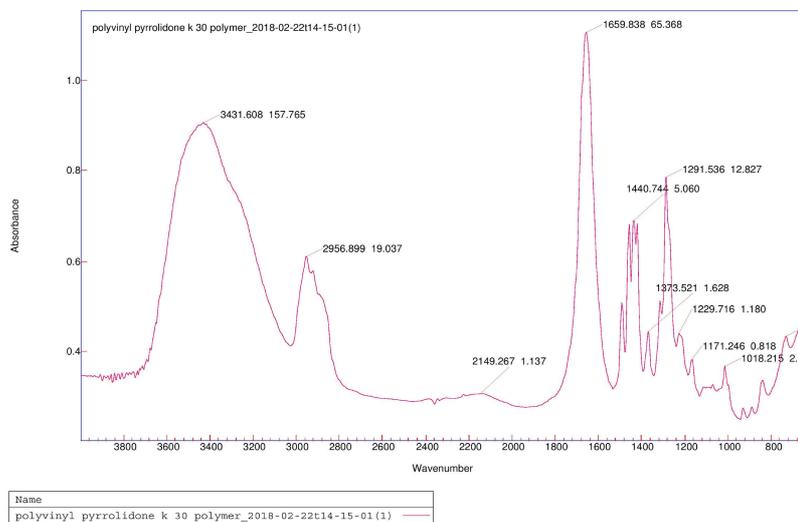


Fig. 3: FTIR for povidone

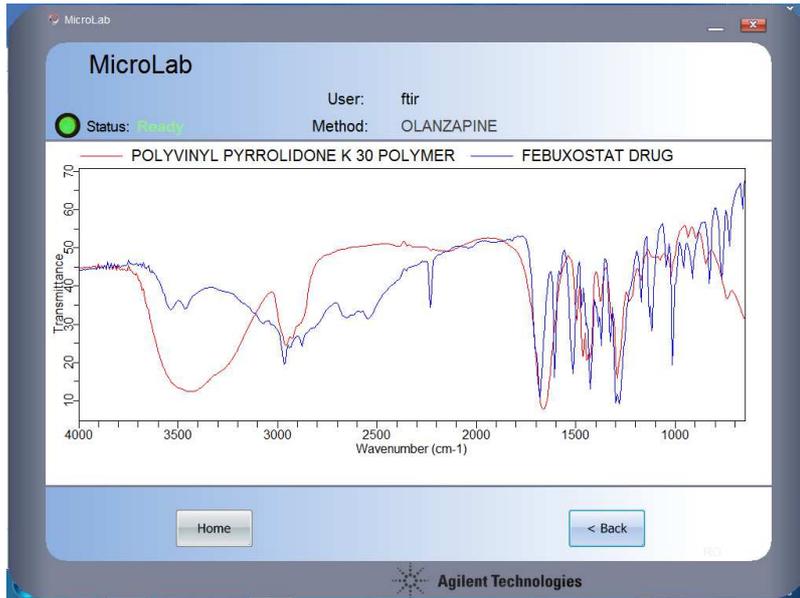


Fig. 4: FTIR for febusostat with povidone

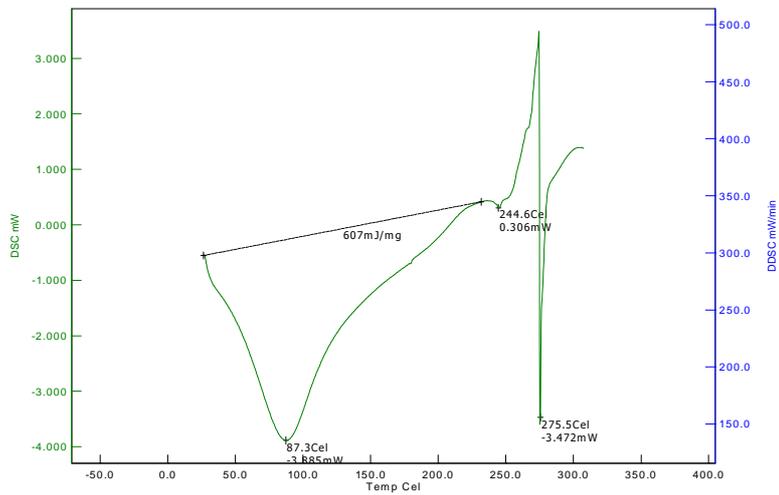


Fig. 5: DSC thermogram for febusostat

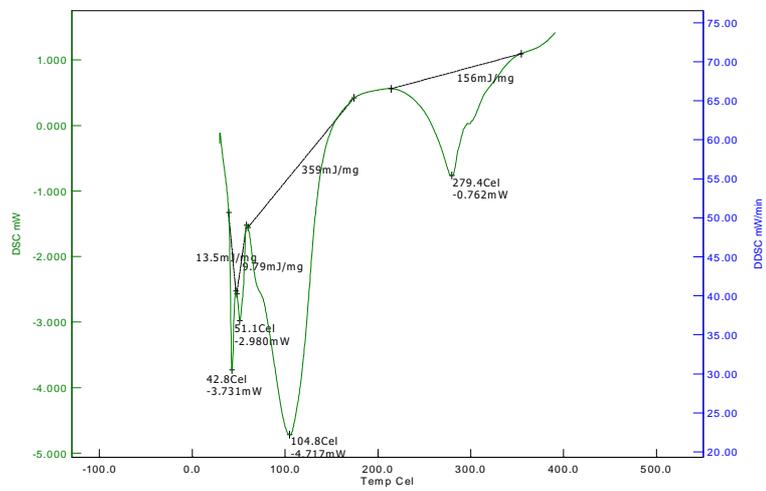


Fig. 6: DSC thermogram for febusostat with polymer in 1:1 ratio

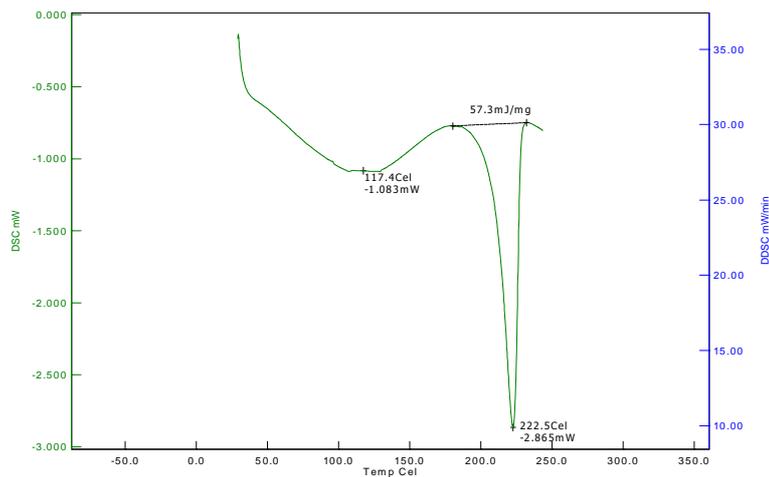


Fig. 7: DSC thermogram for PEG 6000

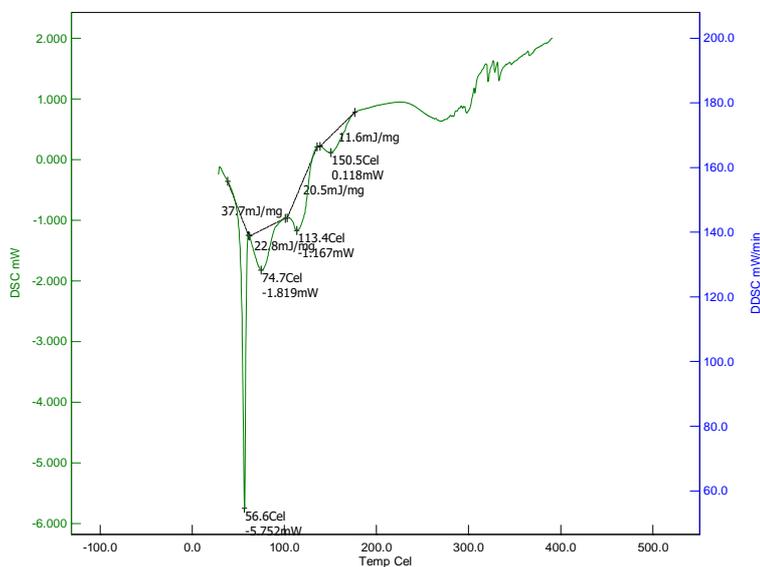


Fig. 8: DSC thermo gram for povidone

Drug-excipient compatibility studies (DSC)

The DSC thermogram shown in fig. 5 to 8, there was a sharp endotherm peak at 87 °C and 275 °C which was shifted to 104 °C and 279 °C when it is combined with the polymer at 1:1 ratio. From the results of pre-formulation studies, it was revealed that there no chemical incompatibility between drug and excipients from DSC studies.

Determination of saturation solubility

The saturation solubility studies is shown in table no. 1. It is found that the solubility of Febuxostat was higher in pH 7.4 phosphate buffer than water. So, pH 7.4 phosphate buffer was chosen as dissolution media for *in vitro* dissolution studies.

Characterization of solid dispersion

Table 3: Characterization of solid dispersion of febuxostat

Formulation code	Percentage yield (% w/w)	Drug content (mg)
FF1	58	43
FF2	64	48
FF3	78	45
FF4	71	51
FF5	54	64
FF6	68	59
FF7	54	62
FF8	74	78

Determination of percentage yield

The percentage yield for various ratios of different drug and polymer were calculated and shown in table 3. The results revealed that the percentage yield was high in 1:4 ratio solid dispersion prepared by solvent evaporation method than compared to the fusion method.

Estimation of drug content in solid dispersion

The drug content for various ratios of different drug and polymer were calculated and shown in table 3. The results revealed that the drug content was high in 1:4 ratio solid dispersion prepared by solvent evaporation method than compared to the fusion method.

In vitro dissolution rate studies on solid dispersions

In vitro dissolution study was carried out with solid dispersions prepared by various methods in various ratios are given in fig. 9. From the results obtained, the percentage drug released at the end of 30 min was found to be high in solid dispersion containing PVP K30 (1:4 ratio) than other solid dispersion of PVP K30 and PEG 6000 in various ratios which may be due to increased entrapment of drug in solvent evaporation method than fusion method.

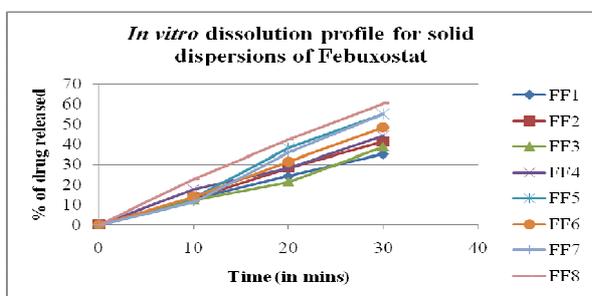


Fig. 9: *In vitro* dissolution profile for solid dispersions of febuxostat (Results are expressed as mean \pm SD, n=3)

CONCLUSION

Febuxostat is a xanthine oxidase inhibitor indicated in patients with gout suffering from hyperuricemia and is used in its chronic

management has low bioavailability when given orally because it is a poorly water-soluble drug with a plasma elimination half-life of 5-8 h. We conclude that the present study of the formulation development for the BCS Class II drug Febuxostat by solvent evaporation method was better than Fusion method in the 1:4 ratio were increase the solubility and dissolution rate.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

Declared none

REFERENCES

- Mohini SP, Sheetal ZG, Saudagar RB. Solubility enhancement by various techniques: an overview. World J Pharm Pharm Sci 2013;2 Suppl 6:4558-72.
- Chaturvedi AK, Verma A. Solubility enhancement of poorly water-soluble drugs by solid dispersion. Int J Pharm Sci Res 2011;3 Suppl 1:26-34.
- Nikita Sehgal, Vishal Gupta N, Gowda DV, Praveen Sivasdasu. Fabrication and evaluation of solid dispersion containing glibenclamide. Asian J Pharm Clin Res 2018;11 Suppl:158-61.
- Gordon LA, Lennernas H, Vinod PS, John RC. A theoretical basis for a biopharmaceutical drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res 1995;12 Suppl 3:413-20.
- Mogal SA, Gurjar PN, Yamgar DS, Kamod AC. Solid dispersion technique for improving solubility of some poorly soluble drugs. Der Pharm Lett 2012;4 Suppl 5:1574-86.
- Sareen S, Mathew G, Joseph L. Improvement insolubility of poor water-soluble drugs by solid dispersion. Int J Pharm Investig 2012;2 Suppl 1:12-7.
- Jatinder Kaur, Geeta Aggarwal, Gurpreet Singh, Rana AC. Improvement of drug solubility using solid dispersion. Int J Pharm Pharm Sci 2012;4 Suppl 2:47-53.
- Indian Pharmacopoeia. The Indian Pharmacopoeia Commission, Ghaziabad. 7th ed; 2014;1:757-8.
- Tripathy S, Sharma PK, Banthia AK. Preparation, characterization, *in vitro* and *in vivo* evaluation of aceclofenac ointment. Indian J Pharm Sci 2005;42 Suppl 9:618-20.
- Asija R, Bhatt S, Sangeetaasija, Shah I, Yadav A. Solubility enhancement of nebivolol by solid dispersion technique. Asian J Pharm Tech 2014;4 Suppl 3:134-40.