Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

Investigation of Impact of Mechanochemical Approach on Solubility and Dissolution Rate Enhancement of Poorly Water Soluble Febuxostat

VISHAL V PANDE, SUREKHA JAMDHADE, GAYATRI V DUSANE,PRIYANKA P SALUNKE,NIKITA A BORAWAKE, PRAKASH N KENDRE*

Department of Pharmaceutics (PG), Sanjivani College of Pharmaceutical Education and Research, Kopargaon

ARTICLE DETAILS

Article history:
Received on 19 May 2017
Modified on 28 June 2017
Accepted on 2 July 2017

Keywords:
Febuxostat,
Mechanochemical approach,
Solid dispersions.

ABSTRACT

The aim of present study was to increase the solubility and dissolution of poorly water soluble Febuxostat by mechanochemical approach. Initially the drug was milled in planetary ball mill and then particle size of milled Febuxostat was measured by Malvern zetasizer, hence the particle size of milled Febuxostat was reduced 4.4% as compare to plain unmilled drug 2%. The solid dispersions of poorly water soluble Febuxostat was prepared with water soluble carrier such as gelucire 44/14 and aeroperl 300 was added as adsorbent to improve its solubility and dissolution properties. The solid dispersions of different ratios i.e., 1:1, 1:2, 1:3 and 1:4 of milled and unmilled Febuxostat were prepared by particle size reduction by planetary ball mill and melt method. Characterization of solid dispersions of milled and unmilled was performed using FTIR, DSC, PXRD, SEM, solubility and dissolution study.

INTRODUCTION

According to International Union of Pure and Applied Chemist (IUPAC) states that "solubility is the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent [1].The basic aim of the further solubility enhancement techniques is to formulate & develop drug to make that drug available at proper site of action within optimum dose [2].

Mechanochemical Approaches [3]

Mechanochemical activation is a practical cogrinding operation used to obtain a solid dispersion of a poorly water soluble drug through changes in the solid state molecular aggregation of drug-carrier mixtures and the formation of noncovalent interactions (hydrogen bonds) between two crystalline solids such as a soluble carrier, and a poorly soluble drug, in order to improve its solubility and dissolution rate.

Author for Correspondence:
Email: prakashkendre@gmail.com

Samples and a physical mixture with a weight ratio were ground using a high speed vibrating ball mill. The ground mixture produced a solid dispersion that had a loss of crystallinity while the drug solubility of solid dispersion increased by as compared to the pure drug.

Mechanochemical activation includes two methods, mechanical and chemical method. For e.g. Mechanical method includes particle size reduction by planetary ball mill and chemical method includes preparation of solid dispersion by melt method. The present study include Investigation of Impact of Mechanochemical approach on solubility and dissolution rate enhancement of poorly water soluble Febuxostat.

MATERIALS AND METHODS

Materials

Drug Febuxostat was received as a gift sample from Celogen Life Sciences, Mumbai, India. Excipients Gelucire 44/14 & Aeroperl300 Pharm, Chemicals & solvents such as Hydrochloric acid, Potassium hydroxide, Sodium hydroxide, Potassium chloride, Potassium Di-hydrogen phosphate & Methanol was purchased from Lobachemie, Mumbai, India.

Methods

Mechanochemical Approach [3]

A. *Mechanical Method*

Febuxostat (5gm) drug was milled at 150rpm for 2hours using planetary ball mill [4]. 2hrs consist of 4cycles each of 30minutes. After completion of one cycle after every 30minutes, 5minutes gap to remove the powder from the wall of vessel with stainless steel spatula for proper grinding.

B.*Chemical Method [5, 6]*

The milled febuxostat drug and gelucire44/14 were accurately weighed in ratio 1:1, 1:2, 1:3 and 1:4. The gelucire44/14 was melted in porcelain dish on heating mental at 50˚C under continuous stirring, and then drug was dispersed into molten gelucire44/14 which was then thoroughly mixed with glass rod and immediately cooled at room temperature to form solid mass. Aeroperl300 was added to solid mass to form free flow solid dispersion. Then it was passed through sieve no. 80 to get uniform particle size.

Drug-Excipients Interaction Study [7]

Drug-excipients interaction study was done by using FTIR spectrophotometer and Differential scanning calorimetry (DSC).

Solubility Study

Solubility Study by Shake Flask Method [8]

Solubility of given below samples was determined by taking an excess amount of sample in 100ml of conical flask which contain 20ml of each solvent system. To minimize photochemical degradation flask were covered with aluminum foil. The flasks were shaken for 48 hours at 37±5˚C in orbital shaker at 55-60 rpm. The solution were transferred to test tubes, and then centrifuged for 15min at 1000rpm. The supernatant of each vials were filtered through whatman filter paper (size 41). An aliquot of each vial was adequately diluted with each solvent system and that appropriate dilution analyzed by spectrophotometric method using a double beam UV-visible spectrophotometer (model-UV 1600S Shimadzu) at 315nm.

Characterization

Particle Size

The mean particle size, particle size distribution and polydispersity index (PDI) were measured by Malvern Mastersizer 2000 (Version 5.22, Serial No. 34027-08, UK).Solid dispersion; milled drug and unmilled drug were suitably diluted with de-ionized water before analysis.

Scanning Electron Microscope (SEM) [9, 10]

SEM is used to examine the surface morphological characteristics and homogeneity of the particles in solid dispersion. Samples were coated with gold-palladium and observed at different magnifications.

Fourier Transform Infrared (FTIR) [7]

The Fourier transform analysis was performed to verify the possibility of interaction between drug and excipients. Fourier- transform infrared spectra of febuxostat drug, milled febuxostat drug, physical mixture, unmilled febuxostat solid dispersion, milled febuxostat solid dispersion were obtained using an FT-IR spectrometer (Shimadzu 8400S, Japan). The small quantity of samples was mixed with KBr to form discs by compressing powders in a hydraulic press, which were analyzed between ranges of 500-3500cm^{-1}.

Differential Scanning Calorimetry [7]

DSC of febuxostat drug, milled febuxostat drug, physical mixture, unmilled febuxostat solid dispersion, milled febuxostat solid dispersion and drug excipient interaction was recorded using differential scanning calorimetry (STAR SW 10.00 instrument). All samples were weighted (1-2 mg) and heated at a scanning rate of 10ºC/min between 0-300ºC with aluminum pans to determine physical or chemical state of materials

Powder X-ray Diffractometer (PXRD)

X-ray powder diffraction pattern of febuxostat and febuxostat solid dispersion was recorded on RigakuUltima (IV) XRD (serial no JD37BD62-3026) make japan diffractometer having Cu-K and #945. The source was operated at 40kV and 40mA.

Determination of drug content

Drug content was determined by dissolving unmilled and milled solid dispersion equivalent to 100 mg in volumetric flask containing methanol and volume was adjusted with methanol up to the mark. Then ultra-sonication was performed to dissolve the drug rapidly in methanol. The resultant solution was then filter through 0.45µ and assayed spectrophotometrically at wavelength 315nm for febuxostat drug content.

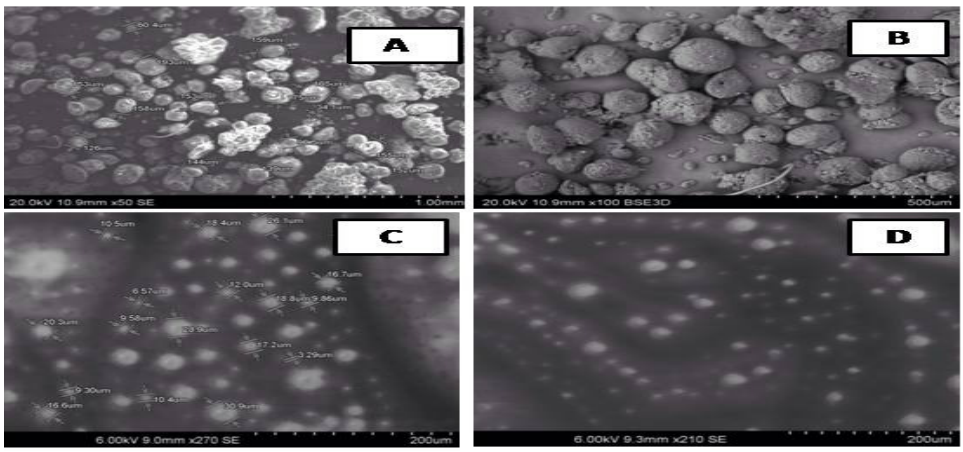

Figure 1: SEM images of- A & B) 1:4 milled Febuxostat solid dispersion, C & D) Milled febuxostat pure drug

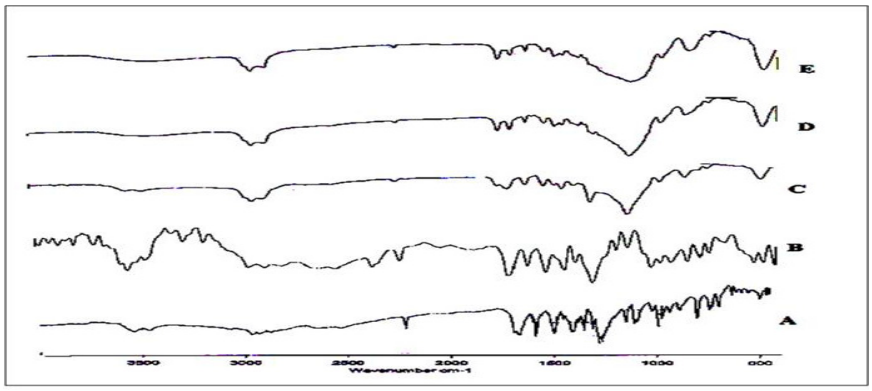

Figure 2: Overlay IR spectra of A) Unmilled drug, B) Milled drug, C) Physical mixture, D) Unmilled S.D, E) Milled S.D.

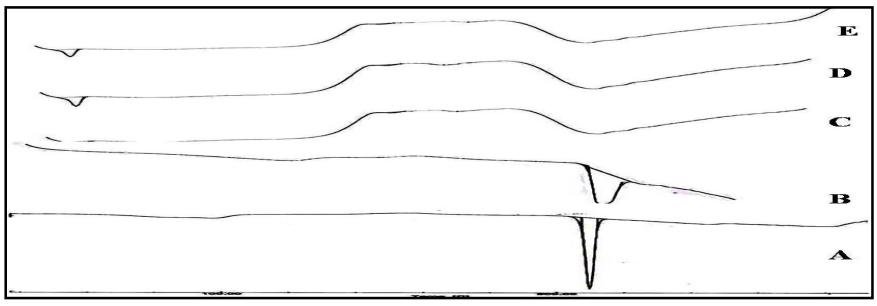

Figure 3: Overlay DSC thermogram of A) Unmilled drug, B) Milled drug, C) Physical mixture, D) Unmilled S.D, E) Milled S.D.

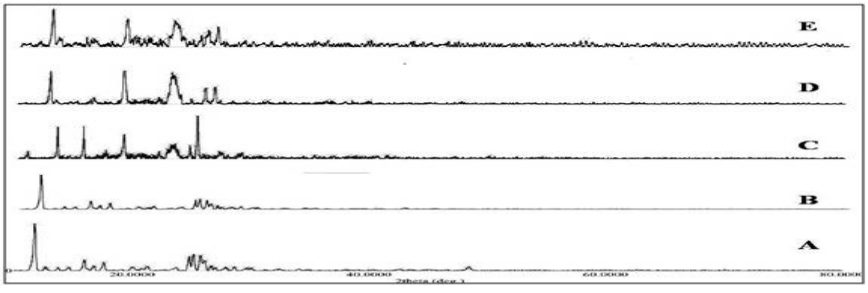

Figure 4: Overlay XRD spectra of A) Unmilled drug, B) Milled drug, C) Physical mixture, D) Unmilled S.D, E) Milled S.D

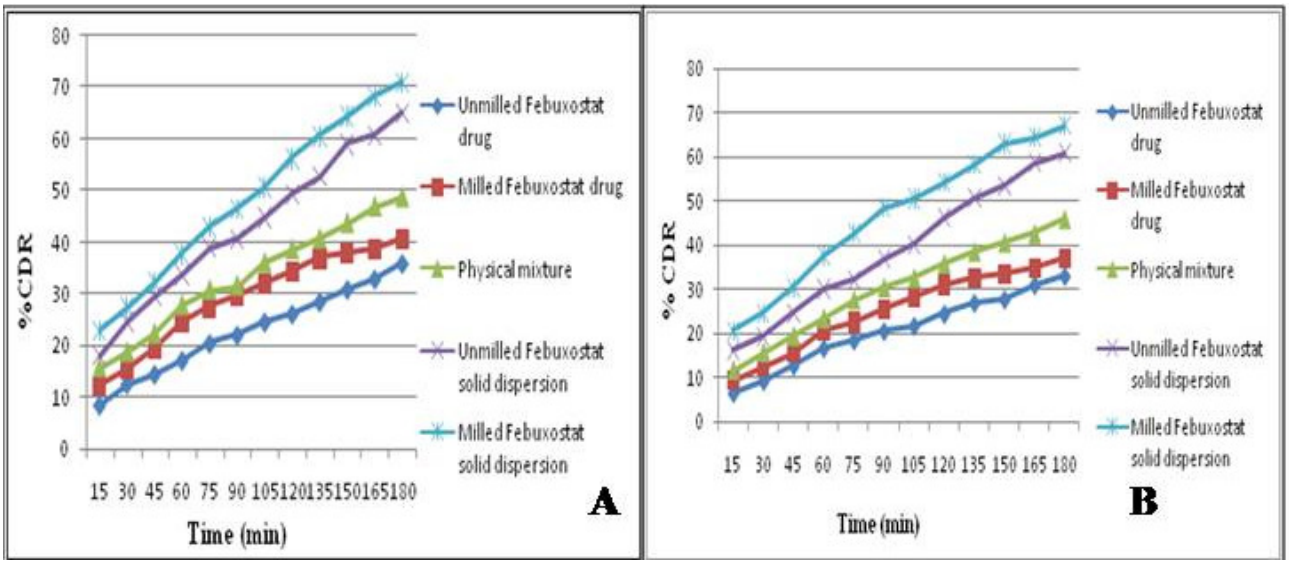

Fig 5(A): Drug release profile of 1:4, ratio solid dispersion in phosphate buffer 6.8
(B): Drug release profile of 1:4, ratio solid dispersion in 0.1N HCl

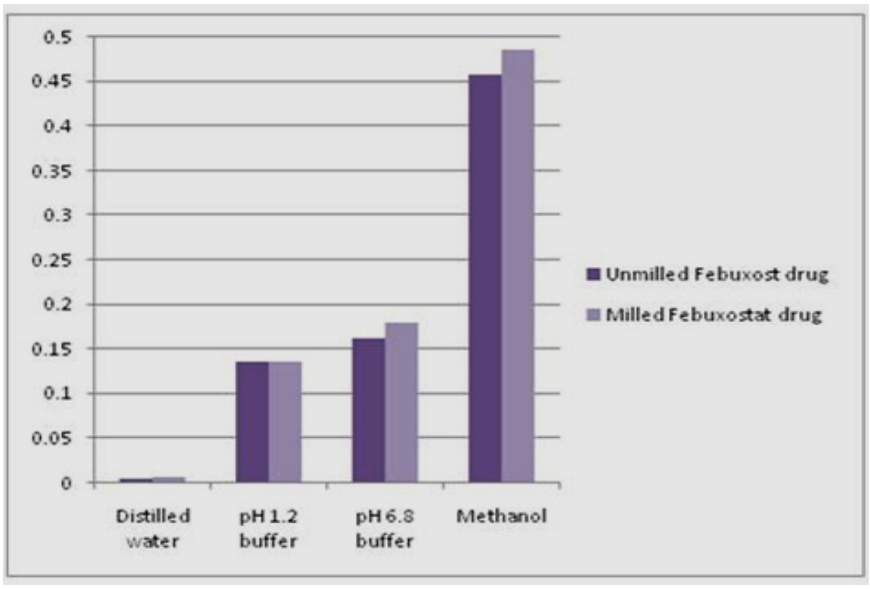

Figure 6: Comparison solubility study of unmilled and milled Febuxostat

Table 2: Solubility study of 1:1 -1:4 ratio solid dispersion

Ratio	Unmilled Febuxostat S.D(mg/ml)			Milled Febuxostat S.D(mg/ml)		
	Water	pH 1.2 buffer	pH 6.8 buffer	Water	pH 1.2 buffer	pH 6.8 buffer
1:1	0.00669	0.19788	0.19788	0.00681	0.20856	0.2381
1:2	0.00707	0.23738	0.23738	0.00831	0.25029	0.26649
1:3	0.00885	0.33257	0.33257	0.00910	0.34738	0.3651
1:4	0.00912	0.3356	0.3356	0.01011	0.41522	0.42332

In–vitro Dissolution Study

In-vitro dissolution study of unmilled febuxostat drug, milled febuxostat drug, physical mixture, unmilled febuxostat drug solid dispersion, milled febuxostat drug solid dispersion were performed using dissolution USP apparatus II. The dissolution medium consisted of 6.8 phosphate buffer and 0.1N HCl. The stirring speed was 75rpm and temperature was maintained at 37±0.5˚C. Powder samples equivalent to 100mg of febuxostat was used for dissolution study. After 15 minute of interval 5ml sample were withdrawn 15, 30, 45, 60,… and replace with same volume of dissolution medium. All the samples were filtered through 0.45µm filter paper. The release of Febuxostat drug was determined by UV spectrophotometer by taking absorbance at 315nm.

RESULTS AND DISCUSSION

Identification and Confirmation of Drug Febuxostat

Confirmation of Febuxostat drug was carried out by using UV spectroscopy, Fourier transform infrared spectroscopy (FTIR) and Differential scanning calorimetry (DSC).

UV Spectroscopy [7]

The calibration curve of Febuxostat was performed in solvents such as water, methanol, 0.1N HCL, phosphate buffer pH 1.2 and pH 6.8 was scanned at 400 nm to 200 nm, an absorbance

Characterization of Solid Dispersion

Characterization of selected ratio of solid dispersion was done by Scanning Electron Microscopy (SEM), Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), and Powder X-ray Diffractometer (PXRD). 1:4 ratio of solid dispersion was selected because it shows increase in solubility than other ratio, as the concentration of polymer increases the solubility increases.

Scanning Electron Microscopy (SEM)

SEM images as shown in **Fig 1** confirmed the homogeneity and surface adsorption of the gelucire 44/14 on aeroperl300 leading to enhanced surface area, dissolution rate and ultimately the bioavailability of Febuxostat drug.

Fourier Transforms Infrared Spectroscopy (FTIR) [7, 11]

The FTIR spectra as shown in **Fig 2** of pure unmilled febuxostat drug and overlapping spectra of physical mixture and solid dispersion there is no significant change in characteristic peaks of pure drug and solid dispersion. So, it indicates that prepared solid dispersion was compatible with excipients.

Differential Scanning Calorimetry (DSC)

From this overlay thermogram of DSC as shown in **Fig 3** it is concluded that A) it shows sharp endothermic peak which indicates that pure drug Febuxostat is in crystalline nature, D) and E) it shows that, in case of S.D the absence of Febuxostat endothermic peak might be due to the formation of solid dispersion in the presence of water soluble polymer where drug could transformed into an amorphous state.

Determination of Drug Content

Drug content was determined by dissolving unmilled and milled solid dispersion equivalent to 100 mg in volumetric flask containing methanol and volume was adjusted with methanol up to the mark. Then ultra-sonication was performed to dissolve the drug rapidly in methanol. The resultant solution was then filter through 0.45µ and assayed spectrophotometrically at wavelength 315nm for febuxostat drug content. Drug content of unmilled and milled Febuxostat solid dispersion was found to be 70% and 76% respectively

PXRD

The XRD spectrum of Febuxostat drug as shown in **Fig 4** shows high intense peak of 2θ value at 11.7800˚, 25.200˚, 24.8200˚, 25.780˚ and 17.620˚ with intensity 10858, 3023, 2749, 2579, and 789 which indicates that the pure drug Febuxostat is in crystalline state.

In vitro dissolution data

The dissolution data of 1:4 ratios, unmilled Febuxostat drug, milled Febuxostat drug, physical mixture, unmilled febuxostat solid dispersion, milled Febuxostat solid dispersion in pH 6.8 buffers and 0.1N HCl is shown in **Fig 5**. As compared to unmilled febuxostat drug, the 1:4 milled Febuxostat solid dispersion shows greater drug release within 180 min i.e. the unmilled febuxostat drug gives 35% drug release whereas milled Febuxostat solid dispersion shows 70% drug release within same period of time in phosphate buffer 6.8 and unmilled febuxostat

drug gives 32% drug release whereas milled Febuxostat solid dispersion shows 66% drug release in 180 minutes in 0.1N HCl. The improved dissolution of milled Febuxostat solid dispersion was observed because of particle size reduction and conversion of crystalline Febuxostat to amorphous form.

Particle Size Determination

Particle size of milled Febuxostat drug (4.4%) and unmilled Febuxostat drug (2%) was reduced after grinding the drug in planetary ball mill.

Solubility Study of Unmilled and Milled Drug

From the comparison of solubility study of unmilled and milled drug it is clear that solubility of milled drug is increased. **(Fig 6 and Table 1**)

Table 1: Solubility of unmilled and milled Febuxostat in different solvents

Sr. No.	Solvents	Solubility unmilled Febuxostat (mg/ml)	Solubility milled Febuxostat (mg/ml)
1	Distilled water	0.0045	0.00531
2	pH 1.2 buffer	0.13219	0.13611
3	pH 6.8 buffer	0.16206	0.17988
4	Methanol	0.45734	0.48535

Solubility study of 1:1to 1:4 solid dispersion

From this comparison solubility study 1:1-1:4 ratio solid dispersion it is clear that solubility increases as the concentration of polymer increases. Therefore it is concluded that 1:4 ratio shows more solubility than other ratio **(Table 2)**.

CONCLUSION

The present work was to enhance the solubility, dissolution and ultimately the bioavailability of Febuxostat by mechanochemical activation. The 1:4 milled Febuxostat solid dispersion enhance the solubility and dissolution of poorly water soluble drug Febuxostat as compared to plain Febuxostat. The Febuxostat solid dispersion with 1:4 ratios was milled and has up to 76% drug loading efficiency. The dissolution release profile of milled Febuxostat solid dispersion was compared with pure crystalline Febuxostat. It concluded that there is improvement in solubility and dissolution behavior due to reduction of particle size, conversion of crystalline to amorphous form.

REFERENCES

[1] Savjani KT, Gajjar AK. Drug solubility: Importance & Enhancement Techniques. ISRN Pharmaceutics. 2012;1-10.

[2] BrahmankarDM. Biopharmaceutics and Pharmacokinetics –A Treatise.Vallabh Prakashan.1st Ed. 282,296-302.

[3] 3.Passerini N, Perissutti B, Albertini B, Franceschinis E. A New Approach To Enhance Oral Bioavailability Of SilybumMarianum Dry Extract: Association Of Mechanochemical Activation And Spray Congealing: Phytomed. 2012;19:160-168.

[4] 4.Radhip NR, Pradeep N, Abhishek AM, et al. Synthesis of Silica Nanoparticles from Malpe Beach Sand using Planetary Ball Mill Method. Journal of Pure Applied and Industrial Physics. 2015;5(6):165-172.

[5] 5.Sridhar I, Doshi A, Joshi B, Wankhede V, Doshi J. Solid dispersion: an approach to enhance solubility of poorly water soluble drugs. J SciInnov Res. 2013;2(3):685-694.

[6] Singh S, Singh R, Yadav L. A review on solid dispersion. Int J Pham Lif Sci. 2011;2(9):1078- 1095.

[7] Pavia DL, Gary ML, George SK. Introduction to spectroscopy, A Guideline for students of Organic chemistry. 3rd Ed.2001;26-61.

[8] Baka E, Krisztina TK. Study of equilibrium solubility measurement by saturation shake flask method using hydrochlorothiazide as model compound. Journal of Pharmaceutical and Biomedical analysis.2008;46:335-441.

[9] 9.Dhirendra K, Lewis S, Udupa N, Atin K. Solid Dispersion: A Review. Pak J Pharm Res. 2009;22(2):234-246.

[10] Kushwaha A. Solid dispersion a promising novel approach for improving the solubility of poorly soluble drugs. Int J Pharm Sci Rev Res. 2011;2:42 -66.

[11] Argade P. S, Magar D. D, Saudagar R B, Solid Dispersion: solubility enhancement technique for poorly water soluble drugs. J Adv. Pharm Educ Res. 2013;3:427-439.