https://doi.org/10.31351/vol33iss(4SI)pp261-270

Preparation and Characterization of Febuxostat as Nanosuspension

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Received 15/4/2024, Accepted 11/8/2024, Published 15/2/2025

Abstract

Febuxostat (FEB) is a potent, non-purine-selective inhibitor of xanthine oxidase used to manage gout. According to the Biopharmaceutical Classification System (BCS), FEB was classified under class II drugs. The drug's low dissolution rate results in a bioavailability of approximately 49%. Drug nanosizing, such as Nanosuspensions (NS), represents an exciting and potentially beneficial method to improve the bioavailability of hydrophobic drugs. This study aimed to prepare and characterize FEB NS to increase the dissolution rate, which can enhance its oral bioavailability. Using solvent/anti-solvent precipitation, 40mg of FEB was dissolved in ethanol and dropped into an antisolvent system containing deionized water, water-soluble stabilizers (L-arginine and Soluplus), and co-stabilizers (Poloxamer 407 and Tween 80) in different ratios. FEB NS formulas were characterized based on particle size (P.S), polydispersity index (PDI), and in vitro dissolution studies. The optimized formula (F7) was further characterized using X-ray diffraction, Fourier transform infrared spectroscopy, and scanning electron microscopy. PDI of 0.13 ± 0.01 and P.S of 62.46 nm ± 0.015 was observed with the selected formula, which contained FEB, Soluplus, and tween 80 in a ratio of (1:4:0.5). A significant increase in drug release was observed at 60 minutes over ordinary FEB suspension. In conclusion, Soluplus was the best stabilizer, and the solvent-antisolvent method used to prepare FEB NS was successful, making NS a valuable approach to improve FEB solubility.

Keywords: Febuxostat, Nanosuspension, Soluplus, Tween 80, L-arginine.

Introduction

The prevalence of hyperuricemia has increased steadily as living standards have improved [(1)]. Gout is a metabolic disease that occurs when monosodium urate crystals accumulate in the body, causing arthropathy. Hyperuricemia is closely related to the development of gout [(2,3)]. Abnormal purine metabolism and decreased uric acid excretion are believed to be the leading causes of hyperuricemia [(4,5)]. Febuxostat (FEB) is a medication used to lower uric acid levels in the body. It selectively inhibits xanthine oxidase, an enzyme that helps produce uric acid. Compared to other drugs, FEB is very effective in improving purine metabolism and enhancing renal protection. The medication is metabolized in the liver and excreted through renal and intestinal pathways after oral administration [(6,7)]. FEB is a chemical compound that is composed of 2-[3-cyanonaphthalenyl]-4-methylthiazole-5-carboxylic acid, as shown in Figure.1[(8)]. It is available in both 40 mg and 80 mg tablet formulations. FEB is administered orally with an initial dose of 40 mg daily [(9)]. With a pKa value of 3.42, this drug is considered a weak acid. It is practically insoluble in water and has a solubility of only 12.9 µg/ml. As a result, it is classified as a BCS class II compound, which means it has low solubility and high permeability. Additionally, FEB reveals poor absorption from the gastrointestinal system, leading to a low oral bioavailability of approximately 49 % [(10)]. Considering FEB's important pharmacological effects and current limitations, there is a large demand for new formulations that can improve its solubility.

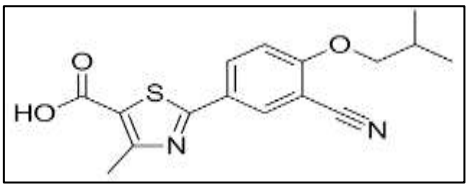

Figure 1. Chemical structure of Febuxostat[(8)]

The pharmaceutical industry and research have faced significant challenges in recent years due to the low water solubility of drug candidates [(11)]. Drug nanosizing, such as NS, is an exciting and potentially useful method to improve the bioavailability of hydrophobic drugs [(12)]. Colloidal dispersions of submicron drug particles are known as nanosuspensions, and they are often described as highly finely dispersed, biphasic colloids containing solid drug particles smaller than one micrometer [(13)]. The pharmaceutical industry has

grown interested in formulating active pharmaceutical ingredients as nanosuspension in the last decade. Some NS products are already available in the market, and many more novel NS are currently being studied by academia and industry [14]. This research aimed to prepare and characterize FEB NS to enhance the solubility and dissolution rate.

Materials and Methods

Materials

FEB powder was supplied by (Bidepharm, China), Soluplus (BASF, Germany), L-arginine (Fluka, Germany), Tween 80 and ethanol (Alpha Chemika, India), and Poloxamer 407 (Sigma Aldrich, Germany).

Methods

Preparation of Febuxostat nanosuspension

A nanosuspension of FEB was prepared through a down-top approach using the solvents/anti-solvents technique. FEB of 40mg was dissolved in 3 ml ethanol, representing a solvent system. The anti-solvent system was composed of 20ml of deionized water, different ratios and types of stabilizers (L-arginine and soluplus) and co-stabilizers (tween80 and poloxamer 407) as shown in Table 1. The organic phase was added drop-wise through a needle with a plastic syringe and directly into a stabilizer solution at room temperature [15]. After adding the organic solvent, the mixture was stirred at a speed of 1000 rpm using a magnetic stirrer for an hour to ensure complete evaporation of the solvent.

Table 1. The Prepared Febuxostat nanosuspension Formulas

Formula code	FEB (mg)	Stabilizer		Co-stabilizer		Stirrer speed
		ARG (mg)	Soluplus (mg)	Tween80 (mg)	Poloxamer407 (mg)	
F1	40	120	-	-	-	1000 rpm
F2	40	160	-	-	-	1000 rpm
F3	40	200	-	-	-	1000 rpm
F4	40	-	120	-	-	1000 rpm
F5	40	-	160	-	-	1000 rpm
F6	40	-	200	-	-	1000 rpm
F7	40	-	160	20	-	1000 rpm
F8	40	-	160	40	-	1000 rpm
F9	40	-	160	-	20	1000 rpm
F10	40	-	160	-	40	1000 rpm
F11	40	-	160	-	-	500 rpm
F12	40	-	160	-	-	1500 rpm

Characterization of the prepared FEB nanosuspension

Particle Size and Polydispersity Index

A particle size analyzer (Malvern Zetasizer Nano Laser, UK) was used to determine the formulations' particle size (P.S) and polydispersity index (PDI). Light scattering from molecules in a sample is measured at a fixed temperature of 25ºC with a 90-degree scattering angle [16].

Determination of drug content in selected FEB NS formulas

One ml of FEB NS was diluted up to 10 ml with ethanol and filtered through 0.45 µm filter paper for assay clarity [17]. The drug content of NS was measured in triplicate using a UV-visible spectrophotometer (Shimadzu, Japan) at λmax of 316 nm. Mean values and standard deviations were reported. Equation (1) was utilized to determine the % drug content.

$$\textbf{Drug content}\ \% = \frac{\textit{Calculated drug content}}{\textit{Theoretical drug content}} \times \textbf{100}\%\ldots.$$ Eq. (1) [18].

In-vitro dissolution studies

In vitro dissolution studies were conducted on ordinary FEB suspension containing (40mg of pure FEB) and the selected formulas using a dialysis membrane with a molecular weight cut-off of 8,000-14,000 Dalton. The membrane was soaked in a pH of 6.8 phosphate buffer for 24 hours before being fixed to the paddle of a USP dissolution device type II. The device was rotated at a speed of 75 rpm in a volume of 900 mL of phosphate buffer with a pH of 6.8; the temperature of the dissolution media was kept constant at 37±0.5°C for the whole duration of the experiment [19]. Samples of 5ml were withdrawn at intervals of 5, 10, 15, 30, 45, and 60 minutes. After each collection, the samples were replaced with an equal volume (5ml) of fresh dissolution medium to maintain the sink condition. The samples were measured at 314 nm UV/Visible spectrophotometer against the blank. The experiments were conducted three times, and the average values were recorded. The absorbance

values obtained were used to calculate the drug release percentage and plotted on a graph over time in minutes [20]. To find comparable dissolution profiles and statistically evaluate the data obtained from dissolution studies, the similarity factor (f2) was employed (equation 2).

$$\mathbf{f2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}|R_t - T_t|^2\right]^{-0.5} \times 100\right\}} \text{ ….Eq. (2)}$$

As shown in the equation above, the parameters (n), (R_t), and (T_t) indicate the number of dissolution time points, the reference dissolution value at a given time (t), and the test dissolution value at that same time (t), respectively. The two dissolution profiles are similar if the f2 values exceed 50. However, the profiles are not identical if the f2 values are less than or equal to 50 [21].

Freeze-drying of the selected FEB NS formula.

The selected FEB NS formula (20ml) was freeze-dried using a lyophilizer (Christ Alpha 1-2 LD Plus). Mannitol, at a concentration of 2% w/v, was employed as a cryoprotectant. The process lasted for 48-72 hours, at a controlled temperature of -44 °C, and the pump operating at a pressure of 2.5 ×10 Pascal[22]. The resulting powder was stored in glass vials at room temperature until further analysis.

Powder X-ray diffractometry (PXRD)

The XRD-6000 (Shimadzu-Japan) was utilized to analyze the patterns of pure FEB, a physical mixture (PM), and the selected formula. The scanning process consistently includes a range of 5-80 degrees. The operation's voltage was adjusted to 40 kilovolts (kV), while the current was adjusted to 30 milliamperes (mA). The scanning step size and duration were set at 0.050° (2θ) and 60 seconds, respectively [23].

Determination of Fourier Transform infrared spectroscopy (FTIR)

The FTIR analysis aimed to identify any interaction or complexation between FEB and the excipients used in the nanoparticle formulation [24]. The FEB, PM and the selected formula were measured with an FTIR spectrometer (Shimadzu-Japan), and their wavenumbers were scanned between 4000 and 400 cm^{-1}.

Scanning electron microscopy (SEM)

The surface morphology of the FEB and the selected formula were analyzed using an Inspect 50 field emission scanning electron microscope (FESEM). The powder was directly deposited on double-sided carbon tape for imaging. Before imaging, a two-minute sputter-coating procedure was performed to ensure the samples were uniformly coated. This procedure involved applying a thin layer to the samples to improve conductivity and enable better imaging [25].

Statistical analysis

The experimental results were presented as the mean ± standard deviation (SD) of three measurements. Statistical analysis was performed by one-way ANOVA test using GraphPad Prism version 8. A significant difference was regarded as ($p < 0.05$).

Results and Discussion

Evaluation of particle size and polydispersity index

The P.S and PDI of FEB NS formulas were measured using Malvern Zetasizer, as illustrated in Table 2. The impact of P.S and PDI was examined across 12 different formulations. A low PDI value signifies a narrow size distribution, indicating a uniform population within the system. Conversely, a PDI value greater than 0.3 suggests a broad size distribution [19]. The formulas F1, F2, and F3 use ARG in three distinct ratios as their primary stabilizer. ARG is a cationic amino acid that provides electrostatic stabilization to the nanoparticle by counteracting the Vander Waals attractions between particles. Additionally, it assists in enhancing the wetting and dispersion of the drug particles, which are typically very hydrophobic [22]. This study found that the P.S and PDI were significantly greater in FEB NS stabilized with ARG compared to those stabilized with Soluplus ($p < 0.05$), as shown in Figure.2 .This can be attributed to the fact that ARG alone is insufficient to stabilize FEB NS and prevent particle agglomeration. All these concentrations of ARG were unable to reduce the particle size. This agrees with the findings of Ain-Ai et al. who used ARG as a primary stabilizer to stabilize naproxen NS. They imply that ARG is not high enough to prevent aggregation and reduce the drug particle size in the suspensions when there is no polymer in the system used [26].In contrast, Soluplus contains amphiphilic groups, such as polyethylene glycol (hydrophilic) and vinyl caprolactam/vinyl acetate (hydrophobic), which help improve surface activity. As a result, Soluplus formulas exhibit smaller PS and more uniform size distribution. Soluplus exhibits superior wettability and steric stabilization compared to other polymeric stabilizers, which is attributed to its bifunctional properties and the large size of its molecule [27]. The best FEB-Soluplus ratio was 1:4 (F5) because it had the smallest particle size and PDI value.

Table 2. The particle size and PDI of Febuxostat nanosuspension formulas

Formula code	Particle size (nm)±SD	PDI±SD
F1	340.3±0.312	0.3767±0.015
F2	473.7±0.208	0.4370±0.001
F3	546.7±0.05	0.4843±0.0015
F4	92.36±0.02	0.4667±0.015
F5	76.05± 0.015	0.1733±0.004
F6	79.23±0.32	0.2673±0.0015
F7	62.46±0.015	0.1300±0.01
F8	82.73±0.208	0.3233±0.002
F9	108.6±0.2	0.2503±0.0175
F10	222.3±0.25	0.3447±0.0041
F11	98.62±0.540	0.446±0.0026
F12	126.7±0.251	0.267±0.002

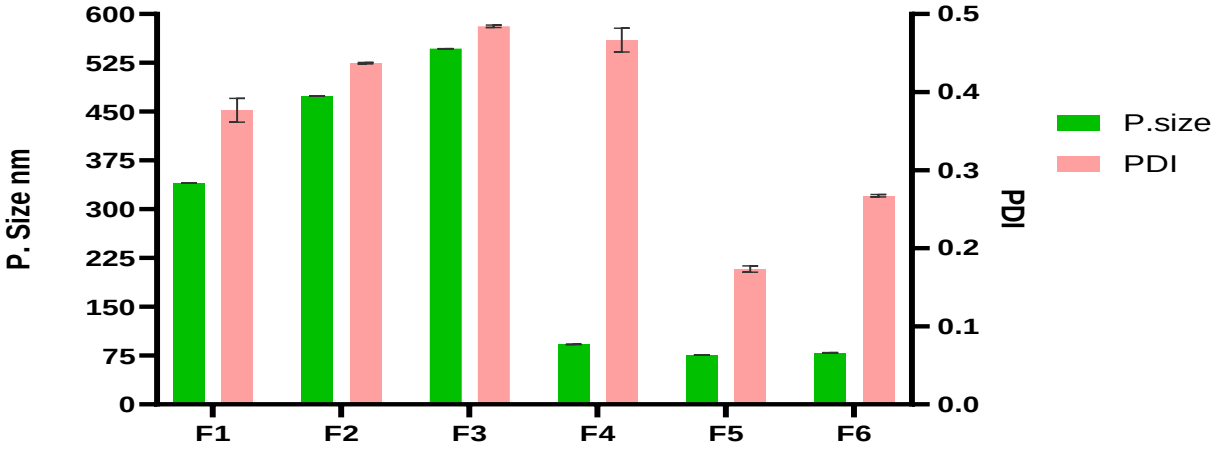

Figure 2. Represent P.S and PDI of FEB NS with different stabilizer types

In F7-F10 formulations, Tween 80 and Poloxamer 407 are used as secondary stabilizers in two ratios. Adding 20mg of Tween 80 significantly ($p<0.05$) reduces P.S and PDI by acting as a non-ionic stabilizer. It creates a physical barrier on the surface to prevent contact with adjacent particles [28]. The F7 has the smallest particle size of 62.46 nm±0.015 and a PDI of 0.13±0.01, making it the most favorable choice. This is due to the combination of soluplus and co-stabilizer tween 80 in a ratio of drug: soluplus: tween80 (1:4:0.5), which reduces the particle size through non-ionic stabilization. This reduction in size provides steric stabilization, which is caused by the adsorbed polymer layer and hydration on particle dispersion and is dominated by the wetting effect [29]. The advantages of steric stabilization are not affected by changes in pH or ionic strength in varying conditions of the gastrointestinal tract [30]. As the amount of tween80 increased, the particle size also increased (F8). A higher concentration of surfactant results in a larger particle size because it causes the thickening of the particle coating and inhibits the diffusion between the solvent and anti-solvent during precipitation [31]. Using Poloxamer 407 as a co-stabilizer in F9 and F10 resulted in a significant increase ($p<0.05$) in P.S and PDI. This indicates that this particular combination was not suitable for FEB NS. The addition of a co-stabilizer may prevent interaction between the drug and stabilizer, leading to an increase in the size of particles, as shown in Figure.3

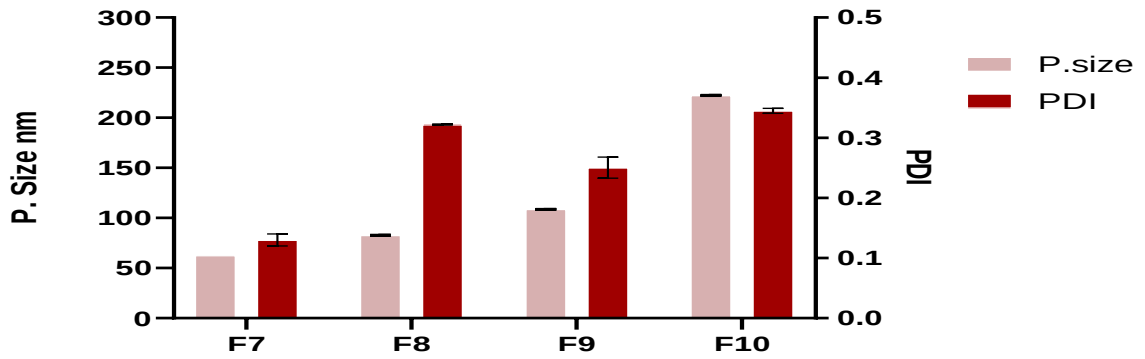

Figure 3. Represent P.S and PDI of FEB NS with different co-stabilizer types

During the formulation process, the speed of the stirrer plays a critical role in determining P.S and PDI; F5, F11, and F12 have different speed rates of 1000, 500, and 1500 rpm, respectively. As depicted in Figure.4, a slower stirring rate from 1000 to 500 rpm significantly increases ($p < 0.05$) in both P.S and PDI. The explanation is that a higher stirring speed (1000 rpm) provides more efficient shear mixing, resulting in a faster diffusion of organic solvent into the water phase. The rapid diffusion of drug particles can lead to rapid nucleation, resulting in the formation of small particles [32]. At 1500 rpm (F12), the PS significantly increases ($p<0.05$) to 126.7±0.25 nm and PDI to 0.267±0.002. This raised stirring speed throughout the formulation process can result in fast nucleation and breakdown of large particles. However, this powerful mechanical stirrer has the potential to supply the system with an excessive amount of energy, which can overcome the barrier made by the stabilizer. Consequently, it may cause a collision between particles, leading to an elevation in the formulation's PS [33].

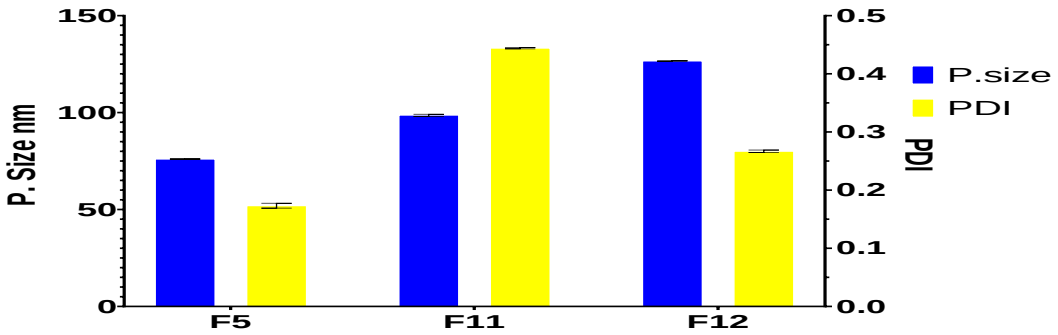

Figure 4. The P.S and PDI of FEB NS at different stirrer speeds

Measurement of drug content in selected FEB NS formulas

The percentage of drug content was calculated only for (F5, F6, and F7) which have P.S of not more than 79.23nm±0.32 and PDI values of less than 0.3. As shown in Table 3, the total drug content of the selected FEB NS formulations exceeded 90% with a low standard deviation value. Therefore, the approach is suitable for reducing particle size.

Table 3. Drug Content of Febuxostat Nanosuspension Formulas

Formula code	%Drug content ±SD
F5	97.13±0.0076
F6	95.53±0.041
F7	98.28±0.104

The in-vitro dissolution study of FEB NS

The dissolution study was carried out in freshly prepared phosphate buffer pH 6.8.After 60 minutes, the percentages of drug release for F5 and F6 were 81.36±1.09% and 83.1±0.85%, respectively, while the ordinary FEB suspension had 40±1%. The increase in dissolution was approximately the same for both formulas due to the proximity of P.S. At the same time, F7 showed a higher dissolution (98.9±1% vs 40±1%) than an ordinary FEB suspension. This can be explained by the Noyes-Whitney equation, which states that the dissolution rate can be improved by increasing the drug particles' surface area (reducing their size) [34]. The statistical analysis indicates that F7 had lower similarity factor (f2= 20.04) than other formulas. Based on the findings of the P.S, PDI, and dissolution studies, F7 is considered the best formula.

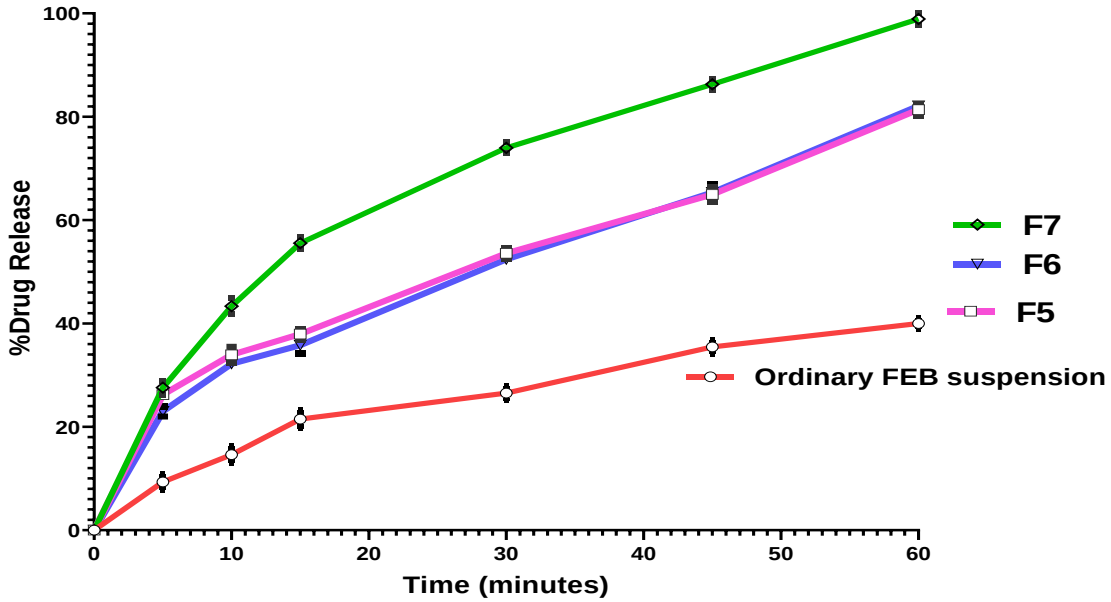

Figure 5. In vitro dissolution profile of FEB NS formulas and ordinary FEB suspension in a phosphate buffer solution pH of 6.8 at 37±0.5°C

Freeze-drying of the selected FEB NS formula.

The lyophilized powder of the selected formula (F7) was used for further characterization analysis. The study included Powder X-ray diffractometry (PXRD), Fourier Transform infrared spectroscopy (FTIR), and surface morphology .

Figure 6. Lyophilized powder of the selected formula (F7)

Powder X-ray diffractometry

The X-ray diffractograms of FEB, PM, and the selected formula (F7) are displayed in Figure.7 .FEB displayed sharp, distinct peaks at theta (2θ) values of 6.6°, 7.2°,12.9°, 13.3°, 16.2°,16.6°, 23.1°, 23.9°, 24.8°, 26.0° and 26.8°, indicating its crystalline nature [19]. The peaks characteristic of FEB were found in PM. However, the intensity of these peaks may have been reduced due to the presence of added excipients. The PXRD spectra of the F7 formulation showed a less intense hollow peak, indicating a possible increase in the drug's amorphous nature compared to the pure crystalline drug.

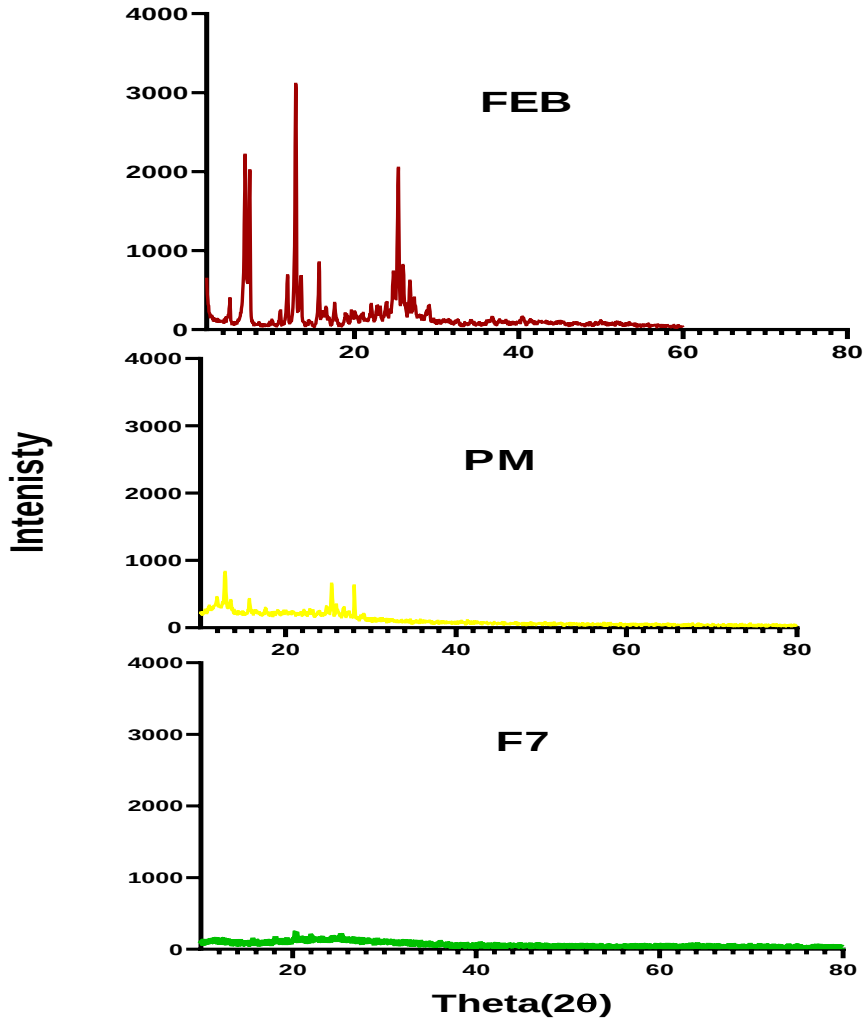

Figure 7. PXRD of FEB, PM, and selected formula F7

Determination of Fourier Transform infrared spectroscopy

The interaction between the drug and excipients was assessed using an FTIR study; Figure. 8 presents the FTIR spectra of FEB, PM, and the selected formula. The pure drug's spectrum exhibited distinct bands at specific wavenumbers: 3546.97 cm^{-1} for O-H stretching, 2956 and 2873 cm^{-1} for C-H stretching of alkane, 2229 cm^{-1} for C≡N stretching, 1680.21 cm^{-1} for C-O stretching of carboxylic acid, and 1512.33, 1579.63, and 1425.4 cm^{-1} for C=C stretching of the aromatic ring [35]. The PM and F7 samples exhibited distinct bands of pure FEB, indicating compatibility and the absence of any notable interaction between FEB and the stabilizer. The presence of hydrogen bonding interactions between water molecules or water and other functional groups in the formulation was indicated by a broad peak between 3200 cm^{-1} and 3600 cm^{-1} [36].

Surface morphology

The photos illustrated the surface morphology of FEB and the selected formula. As represented in Figure.9, FEB had a distinct crystalline arrangement and a nearly flat, plate-like morphology. On the other hand, (Figure.9B) demonstrates that the selected formula showed a noticeable change in surface morphology. The particles exhibited a near-spherical shape and displayed a uniform distribution of sizes within the nanometer scale.

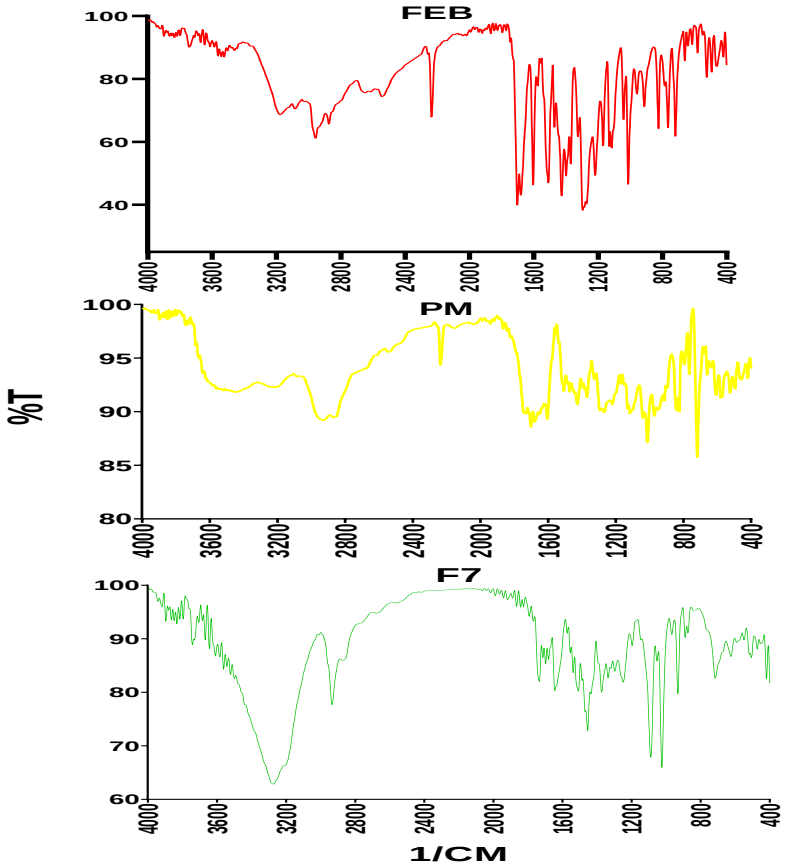

Figure 8. FTIR spectrum of FEB, PM, and selected formula F7

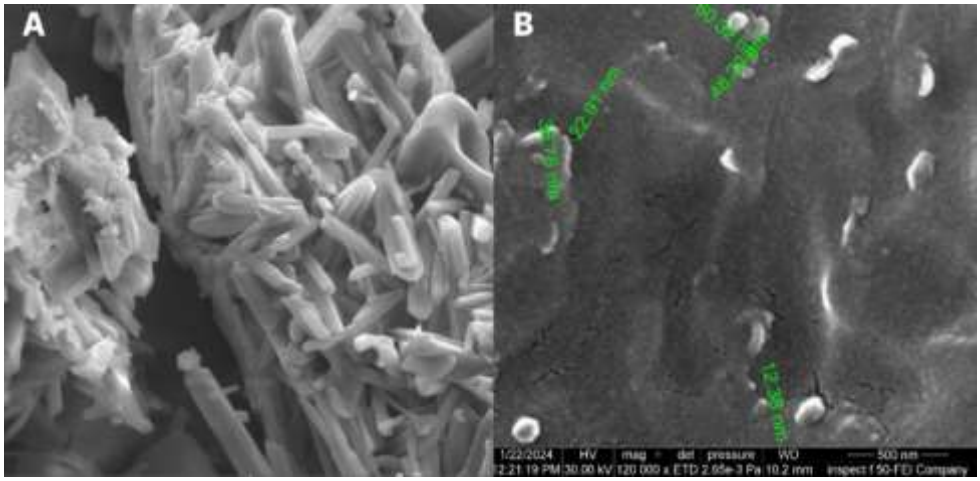

Figure 9. SEM images of (A) FEB and (B) Selected formula F7

Conclusion

In this study, a nanosuspension of febuxostat (FEB) was successfully prepared using a solvent anti-solvent technique with Soluplus as the stabilizer. The selected formula had acceptable particle size (P.S) and polydispersity index (PDI). Therefore, nanosuspension could be a promising approach to improve the solubility of FEB, with a further increase in dissolution and possible improvement in bioavailability.

Acknowledgment

The Department of Pharmaceutics and the College of Pharmacy, University of Baghdad, are to be thanked for their generous assistance in providing the necessary equipment to complete this project.

Conflicts of Interest

There is no conflict of interest.

Funding

There were no specific funds we received from an institution.

Ethics Statements

No animal or human samples were involved in this study.

Author Contribution

The authors confirm their contribution to the paper as follows: study conception and design: Nawal Ayash Rajab, Zahraa Saim Alwan; data collection and draft manuscript preparation: Zahraa Saim Alwan; analysis and interpreted the results: Nawal Ayash Rajab, Zahraa Saim Alwan. All authors reviewed the results and approved the final version of the manuscript.

References

1. Chen Y, Yang Y, Zheng Z, Wang H, Wang X, Si Z, et al. Influence of occupational exposure on hyperuricemia in steelworkers: a nested case-control study. BMC Public Health. 2022; 22(1):1–12.
2. Weaver JS, Vina ER, Munk PL, Klauser AS, Elifritz JM, Taljanovic MS. Gouty Arthropathy: Review of Clinical Manifestations and Treatment, with Emphasis on Imaging. J Clin Med.2021; 11(1):1–28.
3. Li L, Zhang Y, Zeng C. Update on the epidemiology, genetics, and therapeutic options of hyperuricemia. Am J Transl Res. 2020; 12(7):3167–81.
4. Chang Y, Yang M, Zhang Y, Xu G, Li Z. Does hyperuricemia correlate with intervertebral disc degeneration? Med Hypotheses. 2020; 140:109673.
5. Bao R, Chen Q, Li Z, Wang D, Wu Y, Liu M, et al. Eurycomanol alleviates hyperuricemia by promoting uric acid excretion and reducing purine synthesis. Phytomedicine. 2022; 96:153850.
6. Yu H, Liu X, Song Y, Cheng J, Bao H, Qin L, et al. Safety and Efficacy of Benzbromarone and Febuxostat in Hyperuricemia Patients with Chronic Kidney Disease: A Prospective Pilot Study. Clin Exp Nephrol. 2018; 22(6):1324–30.
7. Juge PA, Truchetet ME, Pillebout E, Ottaviani S, Vigneau C, Loustau C, et al. Efficacy and safety of febuxostat in 73 gouty patients with stage 4/5 chronic kidney disease: A retrospective study of 10 centers. Jt Bone Spine. 2017; 84(5):595–8.
8. Dontala SVK, Marabathuni VJP, Narapusetty N. Formulation and invitro evaluation of immediate release tablets containing febuxostat. UPI J Pharm Med Heal Sci. 2022; 5(1):01–8.
9. Gray CL, Walters-Smith NE. Febuxostat for treatment of chronic gout. Am J Heal Pharm. 2011; 68(5):389–98.
10. Yin YF, Guo Y, Song WD, Duan XC, Zheng XC, Zhong T, et al. Improving Solubility and Oral Bioavailability of Febuxostat by Polymer-Coated Nanomatrix. AAPS PharmSciTech. 2018; 19(2):934–40.
11. Guner G, Yilmaz D, Yao HF, Clancy DJ, Bilgili E. Predicting the Temperature Evolution during Nanomilling of Drug Suspensions via a Semi-Theoretical Lumped-Parameter Model. Pharmaceutics. 2022; 14(12):1–19.
12. Fuhrmann K, Gauthier MA, Leroux JC. Crosslinkable polymers for nanocrystal stabilization. J Control Release. 2010; 148(1):e12–3.
13. Zhang J, Xie Z, Zhang N, Zhong J. Chapter 13—Nanosuspension drug delivery system: preparation, characterization, postproduction processing, dosage form, and application. In: Andronescu E, Grumezescu AM, editors. Nanostructures for Drug Delivery. Elsevier; 2017: 413–43.
14. Kayaert P, Van Den Mooter G. Is the amorphous fraction of a dried nanosuspension caused by milling or by drying? A case study with Naproxen and Cinnarizine. Eur J Pharm Biopharm. 2012; 81(3):650–6.
15. Lu S, Yu P. Pan, He JH, Zhang S. Shuang, Xia YL, Zhang WL, et al. Enhanced dissolution and oral bioavailability of lurasidone hydrochloride nanosuspensions prepared by antisolvent precipitation–ultrasonication method. RSC Adv. 2016; 6(54):49052–9.
16. Al Hazzaa SA, Rajab NA. Cilnidipine Nanocrystals, Formulation and Evaluation for Optimization of Solubility and Dissolution Rate. Iraqi J Pharm Sci. 2023; 32(4):127–35.
17. Ubgade S, Bapat A, Kilor V. Effect of various stabilizers on the stability of lansoprazole nanosuspension prepared using high shear homogenization: Preliminary investigation. J Appl Pharm Sci. 2021; 11(9):085–92.
18. Khafeef H k., Rajab NA. Eplerenone Crystal Nanosuspension for Solubility Enhancement: Preparation and Evaluation. Maaen J Med Sci. 2023; 2(2):73–80.
19. Ahuja BK, Jena SK, Paidi SK, Bagri S, Suresh S. Formulation, optimization and in vitro-in vivo evaluation of febuxostat nanosuspension. Int J Pharm. 2015; 478(2):540–52.
20. Paswan SK, Saini TR. Comparative evaluation of in vitro drug release methods employed for nanoparticle drug release studies. Dissolution Technol. 2021; 28(4):30–8.
21. Kadhim ZJ, Rajab NA. Formulation and Characterization of Glibenclamide Nanoparticles as an Oral Film. Int J Drug Deliv Technol. 2022; 12(1):387–94.
22. Jassim ZE, Hussein AA. Formulation and evaluation of clopidogrel tablet incorporating

drug nanoparticles. Int J Pharm Pharm Sci. 2014; 6(1):838–51.
23. Abbas IK, Rajab NA, Hussein AA. Formulation and in-vitro evaluation of darifenacin hydrobromide as buccal films. Iraqi J Pharm Sci. 2019; 28(2):83–94.
24. Hussein ZA, A. Rajab N. Formulation and Characterization of Bromocriptine Mesylate as Liquid Self-Nano Emulsifying Drug Delivery System. Iraqi J Pharm Sci.2018; 93–101.
25. Shariare MH, Sharmin S, Jahan I, Reza HM, Mohsin K. The impact of process parameters on carrier free paracetamol nanosuspension prepared using different stabilizers by antisolvent precipitation method. J Drug Deliv Sci Technol. 2018; 43:122–8.
26. Ain-Ai A, Gupta PK. Effect of arginine hydrochloride and hydroxypropyl cellulose as stabilizers on the physical stability of high drug loading nanosuspensions of a poorly soluble compound. Int J Pharm. 2008; 351(1–2):282–8.
27. Sharma OP, Patel V, Mehta T. Design of experiment approach in the development of febuxostat nanocrystal: Application of Soluplus® as a stabilizer. Powder Technol. 2016; 302:396–405.
28. Hanum TI, Nasution A, Sumaiyah S, Bangun H. Physical stability and dissolution of ketoprofen nanosuspension formulation: Polyvinylpyrrolidone and Tween 80 as stabilizers. Pharmacia. 2023; 70(1):209–15.
29. Wang Y, Zheng Y, Zhang L, Wang Q, Zhang D. Stability of nanosuspensions in drug delivery. J Control Release. 2013; 172(3):1126–41.
30. Tuomela A, Hirvonen J, Peltonen L. Stabilizing Agents for Drug Nanocrystals: Effect on Bioavailability. Pharmaceutics. 2016; 8(2):1-18.
31. Liu D, Xu H, Tian B, Yuan K, Pan H, Ma S, et al. Fabrication of carvedilol nanosuspensions through the anti-solvent precipitation-ultrasonication method for the improvement of dissolution rate and oral bioavailability. AAPS PharmSciTech. 2012; 13(1):295–304.
32. Alwan RM, Rajab NA. Nanosuspensions of Selexipag: Formulation, Characterization, and in vitro Evaluation. Iraqi J Pharm Sci. 2021; 30(1):144–53.
33. Rashid AM, Abd-Alhammid SN. Formulation and characterization of itraconazole as nanosuspension dosage form for enhancement of solubility. Iraqi J Pharm Sci. 2019; 28(2):124–33.
34. Michael E. Aulton KMGT. Aulton-Pharmaceutics-The-Design-and-Manufacture-of-Medicines-5th-Edition. Michael E. Aulton KMGT, editor. Vol. 5, Elsevier; 2018:6-17.
35. Kini A, Patel SB. Phase behavior, intermolecular interaction, and solid-state characterization of amorphous solid dispersion of Febuxostat. Pharm Dev Technol. 2017; 22(1):45–57.
36. Alhagiesa AW, Ghareeb MM. Formulation and Characterization of Nimodipine Nanoparticles for the Enhancement of solubility and dissolution rate. Iraqi J Pharm Sci. 2021; 30(2):143–52.

تحضير وتوصيف المعلقات النانوية للفيبوكسوستات

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الخلاصة

الفيبوكسوستات هومثبط لإنزيم (الزانثين اوكسيديز) ويستخدم لعلاج ارتفاع حامض اليوريك في الدم عند المرضى الذين يعانون من داء النقرس. وفقًا لنظام تصنيف المستحضرات الصيدلانية الحيوية ، يتم تصنيف الفيبوكسوستات ضمن أدوية الفئة الثانية ، لذلك فان توافره البيولوجي يقدربحوالي ٤٩٪. ان تصغير حجم جزيئات الدواء وتحضيره كمعلقات نانوية ،تعتبر طريقة مفيدة لتحسين التوافر البيولوجي للأدوية القليلة الذوبان بالماء. تهدف هذه الدراسة الى تحضير ودراسة خواص المعلق النانوي للفيبوكسوستات لزيادة معدل تحرر الدواء. تم تحضير المعلق النانوي بطريقة المذيبات المضادة للمذيبات باستخدام اثنين من المثبتات (سولوبلس وارجنيين) والمثبتات المساعدة (توين٨٠ وبولوكسامير٤٠٧)، واجراء قياس حجم الجسيمات النانوية ومؤثر التشتت المتعدد ودراسة الذوبانية واجريت اختبارات اخرى لتوصيف افضل صيغة كمنظومة حيود الاشعة السينية ومطياف الاشعة تحت الحمراء والمجهر الالكتروني الماسح، فكانت الصيغة السابعة التي تتكون من (الفيبوكسوستات: سولوبلس: توين٨٠)بنسبة (١: ٤:٠,٥) هي الافضل حيث بلغ حجم الجسيمات النانوية ٤٦, ٦٢ نانوميتر±٠,٠١٥ ومؤثر التشتت المتعدد ٠,١٣ ±٠,٠١ وهنالك زيادة كبيرة في معدل ذوبانية الدواء مقارنة بمعدل ذوبانية الدواء كمعلق عادي ، يمكن ان نستنتج ان تحضير المعلقات النانوية للفيبوكسوستات باستخدام تقنية المذيبات المضادة للمذيبات كانت ناجحة ومفيدة .

الكلمات المفتاحية: الفيبوكسوستات، المعلق النانوي، سولوبلس ، توين ٨٠ ، ارجنيين.