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Research Article

Preparation and Characterization of Febuxostat Nanosuspension as Fast Dissolving Oral Film

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Abstract

Background: Quickly dissolved oral films are a widely accepted method of delivering drugs and help patients adhere to treatment regimens. Nanosuspensions (NS) are colloidal dispersions of drug particles with a submicron size, and their large surface area enhances the solubility and dissolution of low-water-soluble drugs. Febuxostat (FXT) is a non-purine xanthine oxidase inhibitor with a low dissolution rate that limits its absorption. ***Objective***: To develop fast-dissolving oral films (FDOFs) containing FXT NS and convert NS into solid dosage forms to ease administration and accelerate drug release. ***Methods***: FXT NS was prepared using Soluplus as a stabilizer and Tween80 as a co-stabilizer through an anti-solvent precipitation technique. We prepared FDOFs using a solvent casting method, utilizing hydrophilic polymers like pullulan, polyvinyl alcohol (PVA), gelatin, and plasticizers like polyethylene glycol (PEG400) and glycerin. The study assessed the film's thickness, weight, folding endurance, drug content, disintegration time, and drug release. We validated the drug's compatibility using FTIR, and conducted a crystallinity study using DSC and X-ray powder diffraction. ***Results***: F4 was the optimized formula prepared using PVA and PEG400. In just three minutes, the F4 dissolution rate increased significantly (99.63% vs. 11.23%) compared to the FXT ordinary film. Also, it had good mechanical properties. ***Conclusions***: FXT NS were successfully loaded into FDOFs with accepted properties.

Keywords: Febuxostat, Fast-dissolving oral films, Nanosuspension, Solvent casting method.

تحضير وتوصيف الشرائح الفموية السريعة الذوبان في الفم للمعلقات النانوية للفيبوكسوستات

الخلاصة

الخلفية: تعتبر الشرائح الفموية السريعة الذوبان بالفم طريقة متقدمة ومقبولة على نطاق واسع لتوصيل الأدوية مما يساعد المرضى على الالتزام بنظامهم العلاجي . المعلقات النانوية تشير الى تصغير حجم الجزيئات للادوية القليلة الذوبان في الماء مما يساعد على زيادة المساحة السطحية للجزيئات وبالتالي زيادة الذوبانية لتلك الادوية .الفيبوكسوستات هومثبط لإنزيم (الزانثين اوكسيديز) ويستخدم لعلاج ارتفاع حامض اليوريك في الدم عند المرضى الذين يعانون من داء النقرس و يمتلك ذوبانية قليلة بالماء، لذلك فان توافره البيولوجي يقدربحوالي 49%. **الهدف**: تحويل المعلقات النانوية السائلة للفيبوكسوستات الى جرعة فموية صلبة عن طريق تحضيرها كشرائح فموية سريعة الذوبان في الفم لزيادة امتثال المريض للدواء بسب سهولة الاستخدام . **الطرق**: تم تحضير المعلق النانوي بطريقة المذيبات المضادة للمذيبات باستخدام المثبت سولوبلس والمثبت المساعد توين80، تم تحضير الشرائح الفموية بطريقة الصب بالمذيبات باستخدام البوليمرات المحبة للماء مثل البولولان وكحول البولي فينيل والجيلاتين، إلى جانب الملدنات مثل البولي إيثيلين جلايكول 400 والجلسرين. وتم تقييم هذه الشرائح الفموية من حيث خصائصها الفيزيائية مثل السُمك، وتباين الوزن، وتحمل الطي، ومحتوى الدواء، ووقت التفكك، وتحرر الدواء في المختبر. تم تأكيد توافق الدواء مع البوليمر المستخدم في التحضير من خلال مطياف الاشعة تحت الحمراء واجريت دراسة منظومة حيود الاشعة السينية لاثبات تحول الدواء في الشريط الفموي الى حالة غير متبلورة. **النتائج**: كانت افضل صيغة هي F4، والتي تم تحضيرها باستخدام كحول البولي فينيل والبولي إيثيلين جلايكول 400. في ثلاث دقائق فقط، زاد معدل تحرر الدواء للصيغة المحسنة بشكل ملحوظ (99.63 مقابل 11.23%) مقارنة بالشريحة الفموية العادية للفيبوكسوستات ولوحظ أنها تتمتع بخصائص ميكانيكية جيدة. **الاستنتاج**: تم تحميل المعلقات النانوية للفيبوكسوستات بنجاح داخل الشرائح الفموية السريعة الذوبان بالفم وكانت تلك الشرائح تمتلك خصائص مقبولة .

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INTRODUCTION

Gout is a chronic form of arthritis that occurs when urate crystals accumulate in joints, cartilage, and tissues [1]. In recent years, the incidence and prevalence of gout have increased due to changes in lifestyle and diet [2]. To treat gout, Febuxostat (FXT) is a new urate-lowering drug that selectively inhibits xanthine oxidase and improves purine metabolism [3]. FXT is a biopharmaceutical classification system (BCS) class II drug with poor solubility in aqueous media and high permeability [4]. Its poor solubility in water presents a significant obstacle to formulation development [5]. This poor solubility results in a poor bioavailability of about 49% [6]. Drug nanosizing through techniques such as nanosuspensions can be a potentially effective method to improve the bioavailability of hydrophobic drugs [7]. Nanosuspensions consist of colloidal dispersions of pure drug particles at the nanoscale that have been stabilized by an appropriate polymer and surfactant [8]. Reducing the size of drug particles increases the surface area, enhancing the dissolution rate. This phenomenon is described by the Noyes-Whitney equation [9]. In the 1970s, fast-dissolving drug delivery systems were developed as a substitute for conventional solid oral dosage forms for patients who suffer from swallowing difficulties, such as children and geriatric patients [10]. This system is made up of FDOF (Fast-Dissolving Oral Film), which includes an active pharmaceutical ingredient (API) that quickly disintegrates and dissolves in the mouth without requiring water or chewing. This process takes less than a minute and ensures that the API enters the bloodstream rapidly, leading to maximum bioavailability [11]. FDOF comprises API, polymer, plasticizer, and sweetener. Depending on the formulation, super-disintegrants may also be included [12]. A hydrophilic film-forming polymer is recommended since FDOF dissolves quickly in the mouth. Commonly used polymers in film formulation include pullulan, gelatin, hydroxypropyl methylcellulose, and polyvinyl alcohol (PVA). Plasticizer is an essential ingredient in the formulation. It plays a crucial role in enhancing the flexibility of the strip and minimizing its brittleness. The plasticizer significantly improves the strip's properties. Glycerin, propylene glycol, and low-molecular-weight polyethylene glycol are commonly used plasticizer excipients [13]. Natural and artificial sweeteners are added to enhance the taste of the product. These agents are usually used alone or in combination with concentrations of 3 to 6% of strip weight, such as mannitol [14]. The current FXT formulations are film-coated tablets and have limited absorption because of their slowest dissolution rate. Hence, this study aimed to directly cast FXT nanosuspension into films while still in suspension form. This method would lead to faster drug release due to the small particle size in the nanoscale range. A rapid breakdown of the film in the oral cavity is intended to facilitate the rapid onset of the drug. Furthermore, it was developed to improve patient adherence by making medication administration easier.

METHODS

Materials

FXT powder was purchased from Bidepharm (China), Soluplus (BASF, Germany), Tween 80 and Ethanol (Alpha Chemika, India), Polyvinyl Alcohol (HIMEDIA, India), Polyethylene Glycols 400 and Gelatine (Fluka AG, Switzerland), Glycerin and Mannitol (Hopkin & Willims, England), Pullulan and Crospovidone (Shanghai-Ruizheng, China).

Preparation of fast dissolving oral films containing FXT NS

The FXT NS was prepared using the anti-solvent precipitation technique. 40 mg of FXT were dissolved in 3 ml of ethanol, representing a solvent system. The anti-solvent system comprises 20 ml of distilled water, 160 mg of Soluplus as a stabilizer, and 20 mg of co-stabilizers tween 80. The organic phase was slowly added dropwise through a needle attached to a plastic syringe and directly into a water solution at room temperature [15].

Table 1: Composition of FXT NS as oral film

Formula code	F1	F2	F3	F4	F5	F6	F7 (Control film)	F8 (Ordinary film)
Febuxostat (mg)	40	40	40	40	40	40	40	40
Soluplus (mg)	160	160	160	160	160	160	160	-
Tween 80 (mg)	20	20	20	20	20	20	20	-
Pullulan (mg)	220	220	-		-	-	-	-
PVA (mg)	-	-	220	220	-	-	220	220
Gelatin (mg)	-	-	-	-	220	220	-	-
Glycerin (mg)	66	-	66	-	66	-	-	-
PEG400 (mg)	-	66	-	66	-	66	66	66
Crospovidone (mg)	16.5	16.5	16.5	16.5	16.5	16.5	16.5	16.5
Mannitol (mg)	16.5	16.5	16.5	16.5	16.5	16.5	16.5	16.5
Vanilla flavor (mg)	11	11	11	11	11	11	11	11

After adding the organic solvent, the mixture is stirred at 1000 rpm using a magnetic stirrer for an hour to ensure solvent evaporation. The solvent casting method was used to prepare films [16]. The polymer and plasticizer were first added to an aqueous solution and stirred magnetically for one hour to form a homogeneous polymeric solution. The remaining excipients, such as mannitol, crospovidone, and vanilla as flavoring agents, were added to the polymeric solution with continuous stirring. After that, the FXT NS (equal to 40 mg of FXT) was added to

the polymeric solution and stirred for an additional hour. The mixture was left overnight to remove any trapped air bubbles. It was then poured into a square silicon mold measuring 2.3 x 2.3 cm^2 and dried in an oven at 40 °C. After processing, the films were removed from the mold, carefully wrapped in aluminum foil, and kept aside for further evaluation [17]. A control film of FXT (F7) was prepared by adding soluplus and tween80 to an aqueous solution of film additives, and then FXT was added to this mixture. While the ordinary film (F8) was prepared in a similar way without Soluplus and Tween80, as illustrated in Table 1, All prepared films were inspected visually to check their color, clarity, flexibility, and smoothness [18]. The film thickness was determined using a digital Vernier scale to measure the dimensions of the film in both the central region and the four corners [19]. The individual film was weighed using a digital balance, and the average weight was calculated [20]. The surface pH of fast-dissolving strips should be evaluated, as it can induce adverse effects on the oral tissue [21]. The pH of the oral film was determined by putting the strips in a petri dish containing two milliliters of deionized water. Subsequently, the pH of the resultant solution was determined at room temperature using a digital pH meter [22]. Folding endurance refers to the flexibility of a film, that is, its ability to withstand being folded repeatedly without tearing or breaking. The folding endurance of a film can be determined by the number of times it can be folded [20].

Drug Content

The drug content present in FXT films was analyzed through the UV spectrophotometric method [23]. A 10 ml solution of ethanol was added to the film. It was allowed to dissolve over the night. Finally, ethanol was used to dilute the solutions after they had been filtered [24]. The UV absorbance of the filtrates was subsequently determined at a wavelength of 316 nm using a UV spectrophotometer (Shimadzu, Japan).

In vitro disintegration test

The Petri dish method was employed to assess the disintegration time of oral films. Three films from each batch were randomly selected and placed in a beaker with 10 ml of phosphate buffer with a pH of 6.8. The time it took for the films to disintegrate into tiny particles was measured and analyzed in triplicate to determine the average time in seconds (sec) [25].

In vitro drug release

The release performance of FDOF was tested in a USP type II dissolution apparatus with a paddle stirrer rotating at 75 rpm. The dissolution medium for the test was 900 ml of phosphate buffer (pH 6.8) at a temperature of 37 °C±0.5 °C [26]. A 5 ml sample was taken and then substituted by an equivalent amount of phosphate buffer pH 6.8 every 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 15 minutes to maintain a sink condition. The withdrawn samples were then analyzed using spectrophotometry at a wavelength of 314 nm. The experiment was performed three times, and the percentage of drug release was measured.

Drug compatibility study

The analysis was done using an infrared spectrophotometer (Shimadzu, Japan). Two to three mg of samples were combined with 100 mg of potassium bromide powder. Afterward, the blend was compacted into transparent discs and scanned from 4000 to 400 cm^{-1} [10]. The IR spectra were obtained for pure FXT, PVA, and a physical mixture of FXT and PVA in a 1:1 ratio. The physical state of the FXT was analyzed using Differential Scanning Calorimetry (DSC) and X-ray Powder Diffraction (XRPD). DSC thermograms were obtained using a Shimadzu DSC-60 differential scanning calorimeter for FXT, PVA, and a 1:1 physical mixture of FXT and PVA. An aluminum pan with an accurately weighed sample (2-4 mg) was heated at 10 °C per minute through a temperature range of 25–300 °C while being purged with nitrogen (100 ml/min) [23]. The XRPD-6000 (Shimadzu, Japan) was utilized to analyze the patterns of FXT, a physical mixture, and the film of the optimized formula. This study analyzed samples using a Cu Ka X-ray source in a 10-80º range to record the diffraction peak and plot the XRD map [27].

Statistical analysis

The dissolution data was analyzed using the DDSolver® add-in program. The results of experimental data were presented as mean ± standard deviation (SD) of three measurements.

RESULTS

The formulation of FXT NS as FDOFs involved using two types of plasticizers for each polymer, and the physical appearance was examined. Only the F4 and F5 films were clear and homogeneous with a smooth surface. The drug was evenly distributed without any deformities or air bubbles. Gelatin films tend to have a yellowish tint due to the slight yellow color of the gelatin itself, as illustrated in Figure 1.

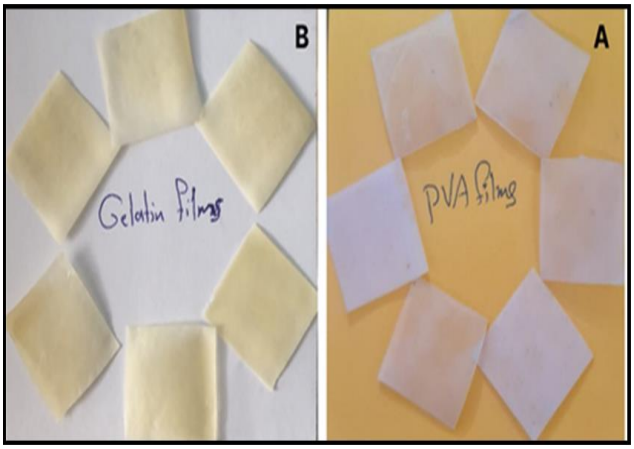

Figure 1: (A) F4 films, (B) F5 films

The thickness of the prepared oral film ranged from 0.33±0.01 mm for F8 to 0.53±0.021 mm for F5, and the weight of these films ranged from 364.7±1.5 mg to 551.0±1.7 mg, as shown in Table 2.

Table 2: Physicochemical parameters of FXT NS as fast-dissolving films

Formula code	Thickness (mm)	Weight (mg)	pH	Folding endurance	DT (sec)	Drug content (%)
F4	0.50±0.01	548.7± 1.15	6.8±0.1	>300	29.33±0.57	99.83±0.8
F5	0.53±0.02	551.0± 1.7	6.33±0.15	>300	37±1	101±1
F7	0.51±0.01	547.3± 2.5	6.4±0.1	>300	35.33±1.5	99.53±0.5
F8	0.33±0.01	364.7±1.5	6.7±0.1	>300	34.67±1.5	98.67±2

Values are expressed as mean±SD.

F8 (ordinary film) weighs the least (364.7±1.5 mg) due to the absence of nanosuspension components (soluplus and tween80). Acidic or basic pH levels cause oral mucosal irritation, so the surface pH should be evaluated. In this study, the prepared films' pH range was between 6.33±0.15 and 6.8±0.1, and this pH range is within the range of salivary pH, which is from 6.2 to 7.4. All prepared formulas exhibited a folding endurance value of over 300, indicating good film flexibility. The acceptable range for content uniformity is between 85% and 115% [28]. The prepared film exhibits a drug content ranging from 98% to 101%, thereby satisfying the requirement for content uniformity. By using a modified petri dish method, the in vitro disintegration time of the formulations varied from 29.33±0.57 to 37±1 seconds , as demonstrated in Table 2. Using a USP type II dissolution apparatus, the in vitro dissolution of FXT NS as FDOF was investigated in phosphate buffer at pH 6.8. The percentage release for different formulations is shown in Figure 2.

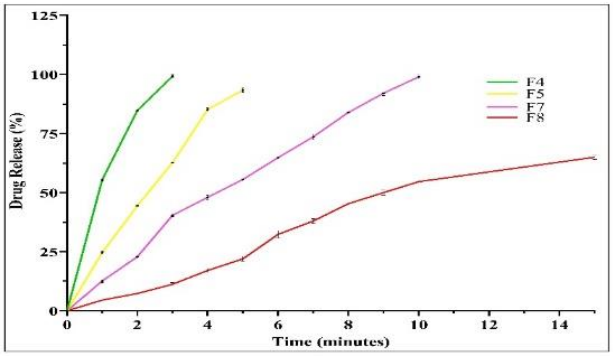

Figure 2: Dissolution pattern of FXT NS as FDOFs at 37°C±0.5°C in phosphate buffer pH 6.8.

In three minutes, F4's dissolution rate increased (99.63 0.63% vs. 11.23 0.68%) compared to FXT's ordinary film. Dissolution profiles with f2 values greater than 50 are likely to be similar. Nevertheless, the profiles are different when f2 values are below or equal to 50 [16]. In comparison to the FXT ordinary film, F4 exhibited a similarity factor (f2 = 19.28) and a superior release profile. F7, the control FXT film, showed 40.4±0.52% release at three minutes, which is faster than ordinary FXT film; the similarity factor between F7 and F8 was (25.02). After analyzing the results of the dissolution study and considering other physicochemical parameters of the film, it was found that the best formula was F4, which is a PVA film. A drug-polymer compatibility study was conducted to provide further characterization of the selected formula. The FTIR spectra of FXT, PVA, and a mixture of FXT and PVA in a 1:1 ratio were illustrated in Figure 3.

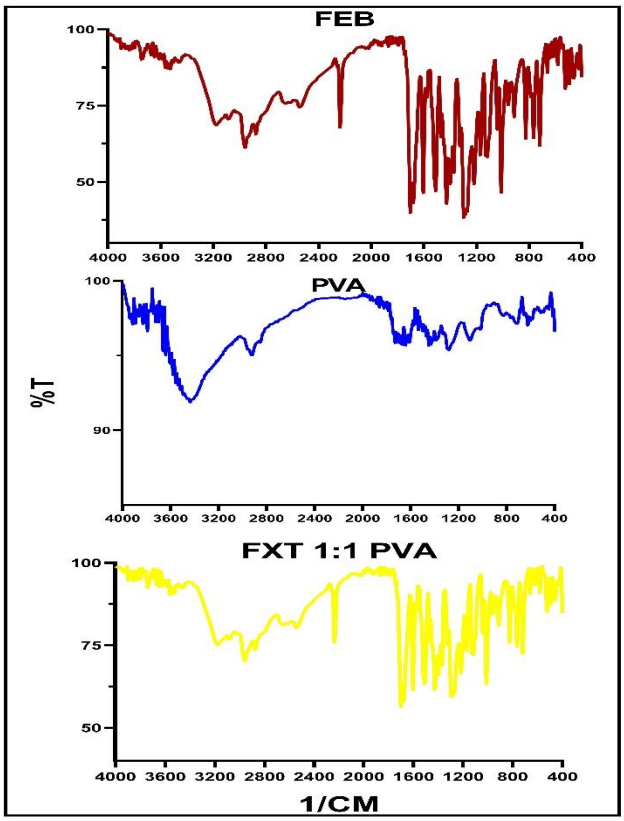

Figure 3: FTIR of FXT, PVA, and a physical blend of FXT and PVA in a 1:1 ratio: (40mg FXT+40mg PVA).

The pure drug's spectrum featured characteristic bands at 3546.97cm^{-1} (O-H stretching), 2938.41, 2959.35 cm^{-1} (C-H stretching of alkane), 2229 cm^{-1} (C≡N stretching), 1680.21 cm^{-1} (C-O stretching of carboxylic acid), and 1512.33, 1579.63 cm^{-1} (C-C stretching), respectively [29]. Large bands can be seen in the PVA spectrum between 3550 and 3200 cm^{-1}. These bands are caused by the O–H stretching through hydrogen interactions within and between molecules. A vibrational band was seen between 2840 and 3000 cm^{-1}, which is caused by the stretching of the C-H group from alkyl groups. The peaks between 1750 and 1735 cm^{-1} are caused by the stretching of the C-O group [30]. Figure 4 shows the DSC thermograms for FXT, PVA, and a physical combination of FXT and PVA in a 1:1 ratio. Looking at Figure 4A, we can see that the FXT had a clear endothermic peak at 205.72 °C.

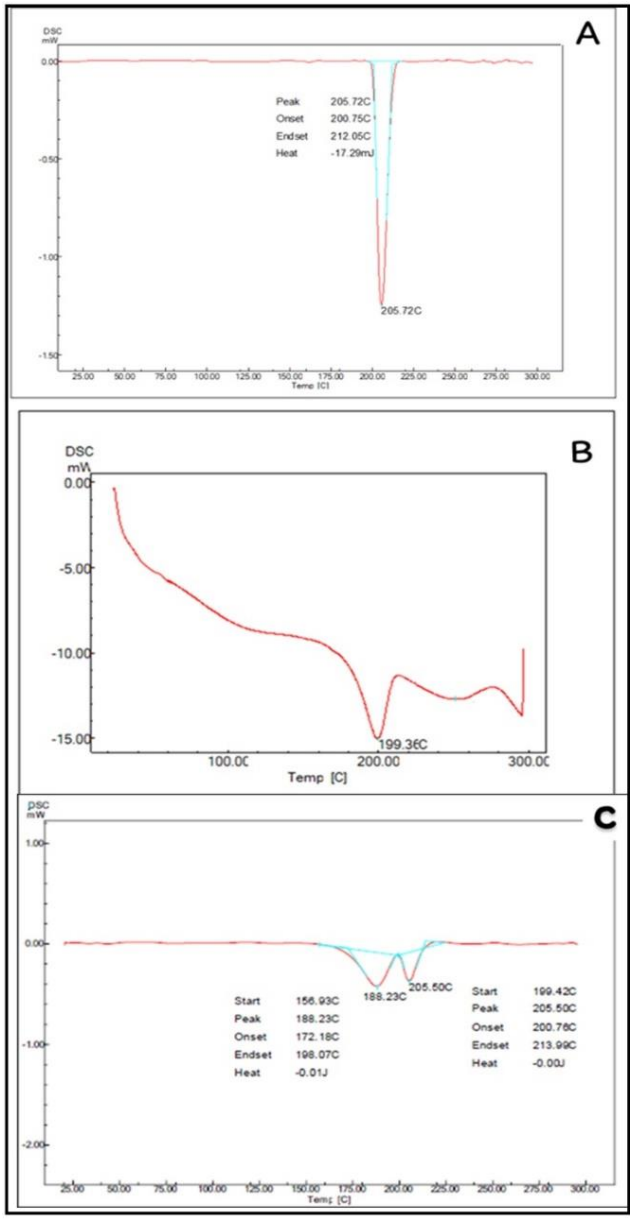

Figure 4: DSC Thermogram of (A) FXT, (B) PVA, (C) physical blend of PVA and FXT in a 1:1 ratio.

According to the literature, FXT melts between 205 °C and 208 °C, which proves that it is pure and real [31]. In Figure 5, X-ray diffraction patterns for FXT, a 1:1 mixture of FXT and PVA, and the optimized formula film (F4) were shown. FXT had sharp, distinct braggs 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 [26]. The physical mixture displayed FXT's characteristic peaks. The presence of PVA in a 1:1 ratio, however, may have reduced the intensity of these peaks. F4 shows the absence of bragg peaks and the appearance of an amorphous halo.

DISCUSSION

The prepared oral film thickness range had a low standard deviation number, showing that the formulation technique is reliable and produces uniformly thick films [28]. The mean weight of the films corresponded to the weight of the original formula, and the pH of the strips was in the range of salivary pH. This indicates that the films are well-suited for oral administration without causing mucosal irritation [32].

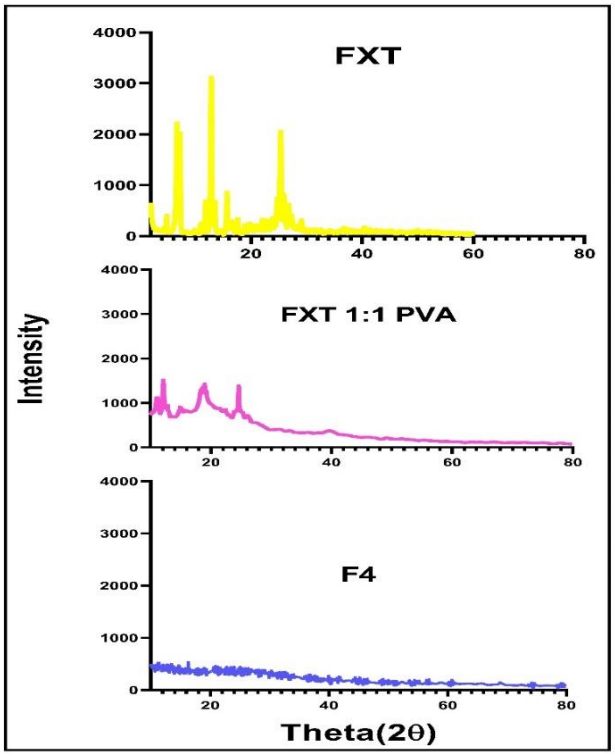

Figure 5: XRPD pattern of FXT, a physical blend of PVA and FXT in a 1:1 ratio and F4 film.

A film with a higher folding endurance value indicates greater mechanical strength. The plasticizer concentration has an impact on the folding endurance value [18]. In this study, the plasticizer concentration was 30% w/w of the polymer weight, which was used to obtain reliable results. The disintegration enhancement is caused by the super disintegrant's ability (crospovidone) to rapidly absorb saliva into the film, resulting in volume expansion and hydrostatic pressures that facilitate rapid disintegration in the mouth [33]. In terms of the dissolution study, F4 had a faster release. This is because it contains FXT particles in a nanosize range; this is described by the Noyes-Whitney equation, which reveals that the dissolution rate can be raised by an increase in the surface area (reducing particle size) of the drug particles [34]. While the release of the control film F7 was higher than the ordinary film due to the presence of soluplus (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer), which is considered a polymer with amphiphilic properties, which was used in the preparation of the oral thin film [24], It possesses dual properties that increase the solubility of poorly soluble drugs through micellization and matrix formation in a one-step preparation [35]. All prominent FTIR peaks of FXT (Figure 3) have been identified and matched with reference spectra, confirming the authenticity of FXT [36]. It is clear that when FXT and PVA are mixed physically in a 1:1 ratio, there are no big

changes in the frequencies of the functional group compared to the pure drug. This means that drug-polymer interaction studies show that FXT was compatible with PVA, which means that the drug and polymer did not interact chemically [37]. The XRPD spectra of the F4 film displayed peaks with a hollow pattern, indicating a higher amorphous content compared to its pure form. This implies that FXT was dispersed in the polymer matrix, in line with the findings of Hadke et al. [38]. This aligns with the results of the dissolution study, which showed that the F4 film had a faster release rate. Therefore, the F4 film is considered to be the optimal formulation. As illustrated in Figure 4C, the physical mixture thermogram also displayed an endothermic peak of FXT at 205 °C, indicating that FXT is still crystalline. Both XRD and DSC studies confirm the crystallinity of pure FXT.

Conclusions

In the solvent casting method, it was possible to successfully add a nanosuspension of Febuxostat to FDOFs using PVA to make a film and PEG 400 as a plasticizer. The F4 film showed acceptable physico-mechanical properties. XRPD studies confirmed that the incorporation of the drug into the oral film transformed its crystalline nature into an amorphous form.

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Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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