

Optimization of Amorphous Solid Dispersion Techniques to Enhance Solubility of Febuxostat

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Abstract

Febuxostat is a selective inhibitor of xanthine oxidase and belongs to BCS class II drugs having low solubility and high permeability. Solubility is the most important parameter which directly affects dissolution, absorption and bioavailability of the drugs. There are different techniques by which we can improve solubility and dissolution rate of poorly soluble drug. Amorphous solid dispersion is one of the methods which can improve solubility as well as powder characteristics. The aim of the present study was to formulate and optimize various methods of formulating solid dispersion by using various drug-to-polymer ratios and identifying the batch which gives higher solubility as well as amorphous powder of the drug febuxostat. Different techniques like hot melt method, solvent evaporation method and spray drying techniques were selected for optimization. Attempts were made to improve solubility of febuxostat by employing Kolliphor P 188, Kolliphor P 237, Eudragit RLPO in different drug-to-polymer ratios (1:1, 1:1.5, 1:2) as carrier. The prepared solid dispersion was characterized for the saturation solubility, percentage yield, using differential scanning calorimetry (DSC), scanning electron microscopy (SEM), powdered X-ray diffraction studies (PXRD), and residual solvent determination. Solid state characterization indicated that febuxostat was present in the amorphous form after mixing with polymeric carrier. In contrast to the pure form of drug, solid dispersion of the drug showed better solubility and amorphous characteristics which can be attributed to decreased crystallinity due to hydrotrophy. Thus, amorphous solid dispersion approach can be used successfully to enhance solubility, dissolution rate and bioavailability of febuxostat.

Keywords

febuxostat, Kolliphor P237, solid dispersion, solubility, spray drying method

INTRODUCTION

Over the years, the majority of compounds have been supplied as a crystalline form due to the high chemical stability, purity and relatively tight packing of molecules in its crystal lattice. Active pharmaceutical ingredient (API) should have sufficient amount of aqueous solubility to dissolve completely in the dissolution media and lipophilicity to pass across the biological membrane.¹ According to

the biopharmaceutical classification system (BCS), class II and IV drugs possess low aqueous solubility and high membrane permeability. Therefore, drugs of these classes phase problems during aqueous dissolution in various manufacturing processes. This hydrophobicity of the drug can be improved by changing the various physicochemical properties of the drug.² Low aqueous solubility of API can be improved by adding surfactants, solubility enhancers, complexing agents, cyclodextrins and forming supersaturated solution of the drug.

Solid dispersion has gained significant importance in the past few years for formulating dosage form of poorly soluble drugs.³ The technique which converts crystalline form of the drug to the amorphous form is known as amorphous solid dispersion (ASD). The amorphous form of the drug has shown better solubility as compared to crystalline form of the drug. The aim of preparing amorphous solid dispersion of the drug is: (I) to improve dissolution rate of the drug and (II) to increase glass transition temperature (T_g) as the higher the T_g the higher the stability of dosages form.

However, the amorphous form is considered thermodynamically unstable because it possesses a high level of energy.⁴ Amorphous solid dispersions have problems regarding stability, hygroscopicity, manufacturing, handling etc. These problems can be overcome by selecting suitable polymer, surfactant, solvents and combining the wise use of manufacturing techniques in the production of ASDs.⁵ Various polymers that have been investigated for drug stabilizing effect includes: PEO-PPO-PEO triblock copolymer, polymethacrylates, polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), methylcellulose (MC), hydroxy propylmethylcellulose (HPMC), hydroxy propyl methylcellulose acetate succinate (HPMCAS), etc. Amorphous solid dispersions can be rendered physically stable via (I) kinetic stabilization, (II) by using low molecular weight highly water-soluble additives, and (III) cellulose polymers and surfactant/polymer-based systems. Surfactants such as tween, labrasol, gelucire, sodium lauryl sulphate, poloxamers have been found to enhance solubility when incorporated in the amorphous solid dispersion.⁶

How ASDs are successful in delaying drug release

Amorphous solid material contained stored potential energy which is released like a spring when the material is dissolved in any media. Therefore, the formulation must provide parachute effect for the production of any delayed or sustained release dosage form. Solubility enhancers or polymers may act like a parachute due to drug polymer interaction in the solution or their adsorption on drug surfaces.⁷ The mechanism of this phenomenon involves reduction in the collision between drug molecules in the solution which inhibits crystallization either by adsorbing to nuclei or causing breakdown of lattice formation.⁸ Different additives like solubilizers, surfactants, wetting agent, complexing agent and foaming agents are used to enhance solubility and they provide parachute effect too. These agents may get adsorb at interfaces and reduces interfacial tension. They may prevent crystallization by inhibiting growth of nuclei. These agents contain hydrophilic and hydrophobic portions in different ratios depending upon which functional group they have.⁹ In the hydrophobic portion they consist of alkyl group, polypropylene oxide, poly ethylene oxide, silicon containing oligomers, fatty acids, bile and salts derived from either natural or

synthetic sources. The polymer provides (I) long term stability to ASD by preventing crystallization and (II) storage stability by inhibiting solid state characterization needed for improvement of bioavailability. Understanding of the physical properties of the drug as well as of the carrier is crucial for the preparation of ASDs.¹⁰

To meet this pharmaceutical challenge, different solubilization techniques have been developed like solid dispersions, nano crystallization, kneading method, spray drying, solvent evaporation techniques, co-precipitation, hot melt method, electrospinning and lyophilization.¹¹ From these techniques, solvent evaporation method, hot melt and spray drying techniques are majorly used in the production of amorphous solid dispersion.¹²

The IUPAC name of febuxostat is 2-[3 cyano-4-(2-methylpropoxy) phenyl]-4-methylthiazole-5-carboxylic acid. It is used in the treatment of hyperuricemia patients.¹³ It is a selective inhibitor of xanthine oxidase/xanthine dehydrogenase. According to the BCS classification, febuxostat is a class II drug which has low solubility and high permeability. The low bioavailability of the drug is due to enzymatic degradation in the intestine and liver. The C_{max} of the drug is decreased by 38-49% in presence of food.¹⁴ The solubility of febuxostat can be improved by forming solid dispersion with different polymers using different solubility enhancement techniques.¹⁵ The solubility of febuxostat is very low in aqueous media and higher in organic solvents, hence it can be used in formulation of amorphous solid dispersion. The solid dispersion system has an option for using lab scale equipment for in-house manufacturing of small batches of drug delivery systems. Thus, bioavailability of the drug can be increased by forming the solid dispersion of that drug.^{16,17}

Herewith, we had attempted to improve solubility of febuxostat by using different polymers (Kolliphor P 188, Kolliphor P 237, Eudragit RLPO) as carriers (in the ratios of 1:1, 1:1.5, and 1:2) and they were prepared using hot melt (fusion) technique, simple solvent evaporation technique and spray drying technique. Kolliphor grades were used to improve solubility of the drug and Eudragit RLPO was used to provide sustained release to the formulation.¹⁸ The prepared solid dispersions were compared with pure febuxostat and the physical mixtures of drug and polymer. The physicochemical properties of solid dispersion were characterized by using differential scanning calorimetry (DSC), powder X-ray diffraction, Fourier transform infrared (FT-IR) spectroscopy, and scanning electron microscopy (SEM), and saturation solubility studies.¹⁹

MATERIALS AND METHODS

Febuxostat was procured from Balaji Drugs, Surat, India. The polymers such as Kolliphor P 188, Kolliphor P 237 and Eudragit RLPO were purchased from BASF/ Sigma-Aldrich, Bangalore. All other reagents used in this research work were of analytical grade.

UV method development

A stock solution of 100 µg/ml of febuxostat (FXST) was prepared by dissolving 10 mg of the drug in a small quantity of methanol and sonicated for a few minutes and diluted with 100 ml of water.²⁰ The stock solution was serially diluted to get solutions in the range of 1-10 µg/ml and the λ_{\max} of the solution was determined. The absorbance of the different diluted solutions was measured in a UV-Visible spectrophotometer at 314 nm.²¹ The absorbance of each serially diluted concentration was taken using UV visible spectrophotometer (UV-1800, Shimadzu, Japan). Finally, calibration curve concentration (µg/ml) versus absorbance was plotted. Regression equation and regression coefficient (R^2) were reported.

Identification of drug-excipients compatibility study by DSC study

Differential scanning calorimetry is widely used in thermal analysis to monitor endothermic processes (melting, solid-solid phase transitions and chemical degradation) as well as exothermic processes (crystallization and oxidative decomposition). It is extremely useful since it indicates the existence of possible drug-excipients or excipient-excipient interactions in formulation. Thermograms of pure drug febuxostat and with excipients used in the formulation were obtained by using differential scanning calorimeter. Samples were weighed directly in pierced DSC aluminium pan and scanned in the temperature range of 50-300°C under an atmosphere of dry nitrogen. Heating rate of 10°C/min was used and thermogram obtained was observed for interaction between drug and excipient.²²

Preparation of solid dispersion

The solid dispersions of febuxostat using different polymers (Kolliphor P 188, Kolliphor P 237, Eudragit RLPO) were prepared using hot melt (fusion) technique, simple solvent evaporation technique as well as spray drying technique.²³ The prepared solid dispersions and the physical mixtures of drug with polymers were compared with pure febuxostat.

Hot melt (fusion) technique

Required quantity of drug and polymers (Kolliphor P 188, Kolliphor P 237, Eudragit RLPO) were grounded together to produce a fine powder and poured onto a glass plate heated to 80°C. The resulting liquid was immediately poured on to the glass plate, maintained at 0°C and allowed to congeal. The powdered solid dispersion was scraped and grounded into a fine powder. The powder was sifted through sieve No. 60. Thus, prepared solid dispersions were stored in a desiccator until further evaluation. The solid dispersion batches prepared by hot melt method were termed as FSD1- FSD9. The composition for all the batches is shown in **Table 1**.

Solvent evaporation technique

In this study, a drug (febuxostat) and different polymers (Kolliphor P 188, Kolliphor P 237, Eudragit RLPO) in different ratios (1:1, 1:1.5, and 1:2) were dissolved in acetone (25 mL) separately to obtain a clear solution. Then, the drug solution was poured into polymeric solution in a mortar and triturated lightly to evaporate acetone slowly. The obtained film was then dried under vacuum until constant weight was achieved and pulverized and sifted through sieve No. 60 to obtain the solid dispersions. The resulting solid dispersion was dried and weighed for further evaluation.²⁴ As shown in **Table 2**, the solid dispersion batches prepared by solvent evaporation method were termed as FSD10- FSD18.

Spray drying technique

Solid dispersions of the drug (febuxostat) in different polymers (Kolliphor P 188, Kolliphor P 237, Eudragit RLPO) in different drug to polymer ratios (1:1, 1:1.5, 1:2) were prepared. The required amount of polymer was weighed and mixed with sufficient quantity of the solvent acetone (200 mL) to obtain a clear solution. Solidification of solid dispersion was achieved using spray drying technique (Model: LU222 Advance, make: Labultima), equipped with a high-performance cyclone. The spray solution was then fed into the heat exchanger using a 3-stage piston mem-

Table 1. Formulation table for solid dispersion using hot melt (fusion) technique

Batch No	Polymer	Ratio (Drug to polymer)	Drug (Febuxostat) (gm)	Polymer (gm)
FSD1		(1:1)	2	2
FSD2	Kolliphor P 188	(1:1.5)	2	3
FSD3		(1:2)	2	4
FSD4		(1:1)	2	2
FSD5	Kolliphor P 237	(1:1.5)	2	3
FSD6		(1:2)	2	4
FSD7		(1:1)	2	2
FSD8	Eudragit RLPO	(1:1.5)	2	3
FSD9		(1:2)	2	4

brane pump at 1 mL/min feed rate. The heat exchanger was heated with steam at 13 bars so that, after overheating, a temperature of 150°C set in. The liquid was then atomized in a spray tower using a hollow cone pressure nozzle (bore diameter 0.6 mm) at a pressure of 100 bars. The spray tower was operated with nitrogen at an inlet temperature

of 140°C and an outlet temperature of approx. 100°C. The spray dried powder was subsequently filtered using a tube filter. Thus, spray dried solid dispersions were collected and stored in a desiccator until further evaluation.²⁵ As shown in **Table 2**, the solid dispersion batches prepared by spray drying method were termed as FSD19- FSD27.

Table 2. Result for % yield of solid dispersion obtained using different methods

Batch No.	Solid dispersion Technique	Polymer	Ratio (Drug to Polymer)	Drug (Febuxostat) (gm)	Polymer (gm)	Yield		
						Theoretical weight (gm)	Weight of SD (gm)	Yield (%)
FSD1	Hot melt (fusion) technique	Kolliphor P 188	(1:1)	2	2	4	3.81	95.14
FSD2			(1:1.5)	2	3	5	4.66	93.23
FSD3			(1:2)	2	4	6	5.59	93.11
FSD4		Kolliphor P 237	(1:1)	2	2	4	3.85	96.25
FSD5			(1:1.5)	2	3	5	4.73	94.58
FSD6			(1:2)	2	4	6	5.64	93.92
FSD7		Eudragit RLPO	(1:1)	2	2	4	3.95	98.86
FSD8			(1:1.5)	2	3	5	4.89	97.71
FSD9			(1:2)	2	4	6	5.77	96.11
FSD10	Simple solvent evaporation technique	Kolliphor P 188	(1:1)	2	2	4	3.61	90.14
FSD11			(1:1.5)	2	3	5	4.41	88.23
FSD12			(1:2)	2	4	6	5.29	88.11
FSD13		Kolliphor P 237	(1:1)	2	2	4	3.65	91.25
FSD14			(1:1.5)	2	3	5	4.48	89.58
FSD15			(1:2)	2	4	6	5.34	88.92
FSD16		Eudragit RLPO	(1:1)	2	2	4	3.75	93.86
FSD17			(1:1.5)	2	3	5	4.64	92.71
FSD18			(1:2)	2	4	6	5.47	91.11
FSD19	Spray drying technique	Kolliphor P 188	(1:1)	2	2	4	2.02	50.47
FSD20			(1:1.5)	2	3	5	2.41	48.16
FSD21			(1:2)	2	4	6	2.73	45.54
FSD22		Kolliphor P 237	(1:1)	2	2	4	2.42	60.5
FSD23			(1:1.5)	2	3	5	2.89	57.73
FSD24			(1:2)	2	4	6	3.40	56.73
FSD25		Eudragit RLPO	(1:1)	2	2	4	2.66	66.52
FSD26			(1:1.5)	2	3	5	3.11	62.21
FSD27			(1:2)	2	4	6	3.63	60.49
FSD28	Physical mixture	Kolliphor P 188	(1:1)	2	2	4	3.98	99.54
FSD29			(1:1.5)	2	3	5	4.97	99.33
FSD30			(1:2)	2	4	6	5.97	99.47
FSD31		Kolliphor P 237	(1:1)	2	2	4	3.97	99.22
FSD32			(1:1.5)	2	3	5	5.00	99.94
FSD33			(1:2)	2	4	6	5.96	99.38
FSD34		Eudragit RLPO	(1:1)	2	2	4	3.97	99.32
FSD35			(1:1.5)	2	3	5	4.99	99.78
FSD36			(1:2)	2	4	6	5.99	99.75

Physical mixture

The physical mixture of drug and polymers in the same ratios were prepared by accurately weighing and thoroughly mixing in a glass mortar 5 min at a mixing speed of 20 rpm. The obtained mixtures were sifted through sieve No. 60 and stored in a desiccator until further evaluation. As per **Table 2**, the batches for physical mixture were indicated as FSD28-FSD36.

Saturation solubility study

The saturation solubility study of febuxostat was performed using shake flask method. The excess amount of drug was allowed to dissolve overnight in 10 ml of distilled water. The resulted solution was filtered through Whatman® filter paper. The filtrate was appropriately diluted using distilled water and the absorbance was taken using UV visible spectrophotometer (UV-1800, Shimadzu, Japan) at 314 nm wavelength.

Residual solvent determination

The residual solvent acetone in the prepared febuxostat solid dispersion (batch No. FSD 24) was analyzed using Shimadzu GC-2014 with headspace auto sampler HT200H gas chromatograph (**Fig. 3**) (Shimadzu, Kyoto, Japan) with DB-624 Fused silica column (30 m long, 0.53 mm internal diameter coated with 3.0 µm film of 6% cyanopropyl phenyl 94% dimethyl polysiloxane) equipped with a G1540N-210 Flame-ionization detector (FID).²⁶

X-RD Study

To evaluate the crystalline state of both pure drug and solid dispersion formulation, powder X-ray diffraction (XRD) study was performed. XRD pattern was recorded using X-ray diffractometer (Xpert Pro MPD, Powder PAN analytical system, Almelo, the Netherlands) with Cu Ka radiation generated at 40 mA, 35 kV and 1.5405 Å wavelength using an accelerator detector with diffracted beam

monochromator. Data was recorded in analytical xrdml file. The results were analyzed using OriginPro2018 software and presented in **Table 5** and **Fig. 6**.

RESULTS AND DISCUSSION

The calibration curve of absorbance versus concentration of febuxostat in methanol was found to be linear over the range of 0.1-0.6 µg/ml for this method. The equation for the linear regression was found to be $Y=0.0516\cdot X+0.0014$, where Y is the absorbance and X is the concentration (µg/ml) of pure drug solution (**Fig. 1**). Linearity of the equation with negligible scattered points has shown that curve did not deviate from the origin. The above-mentioned values of slope and intercept fall within 95% confidence limits. The DSC thermograms for febuxostat and polymers were shown in **Fig. 2**. **Fig. 2A** shows sharp endothermic peak of the drug febuxostat at 201-255°C showing crystalline nature of the drug. **Fig. 2B** shows peaks ranging from 39.63°C to 205°C indicating presence of residual moisture and hygroscopic nature of the drug.

The prepared solid dispersions by different methods were characterized for % yield, which is shown in **Table 2**. It can be observed that in hot melt (fusion), simple solvent evaporation and physical mixture techniques the material loss is quite less as compared to spray drying technique. In spray drying technique the material loss is high due to the large surface area of drying chamber and cyclone separator. The material often gets stuck with surface which cannot be able to recover which could be the reason for low % yield in spray drying technique. In the hot melt technique, the % yield is greater as compared to the spray drying technique but the saturation solubility was found to be low. From solvent evaporation technique, maximum amount of % yield was obtained but due to the risk of residual solvent entrapment, the method is at the least priority.

The data for saturation solubility for all batches (FSD1-FSD36) are shown in **Table 3**. Based on an analysis of saturation solubility study of prepared batches (FSD1-FSD36) of solid dispersions, it can be observed that compared to

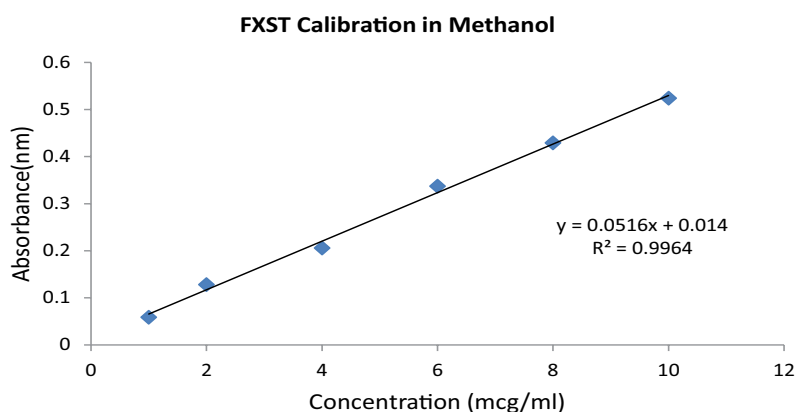


Figure 1. Standard calibration curve of febuxostat in methanol.

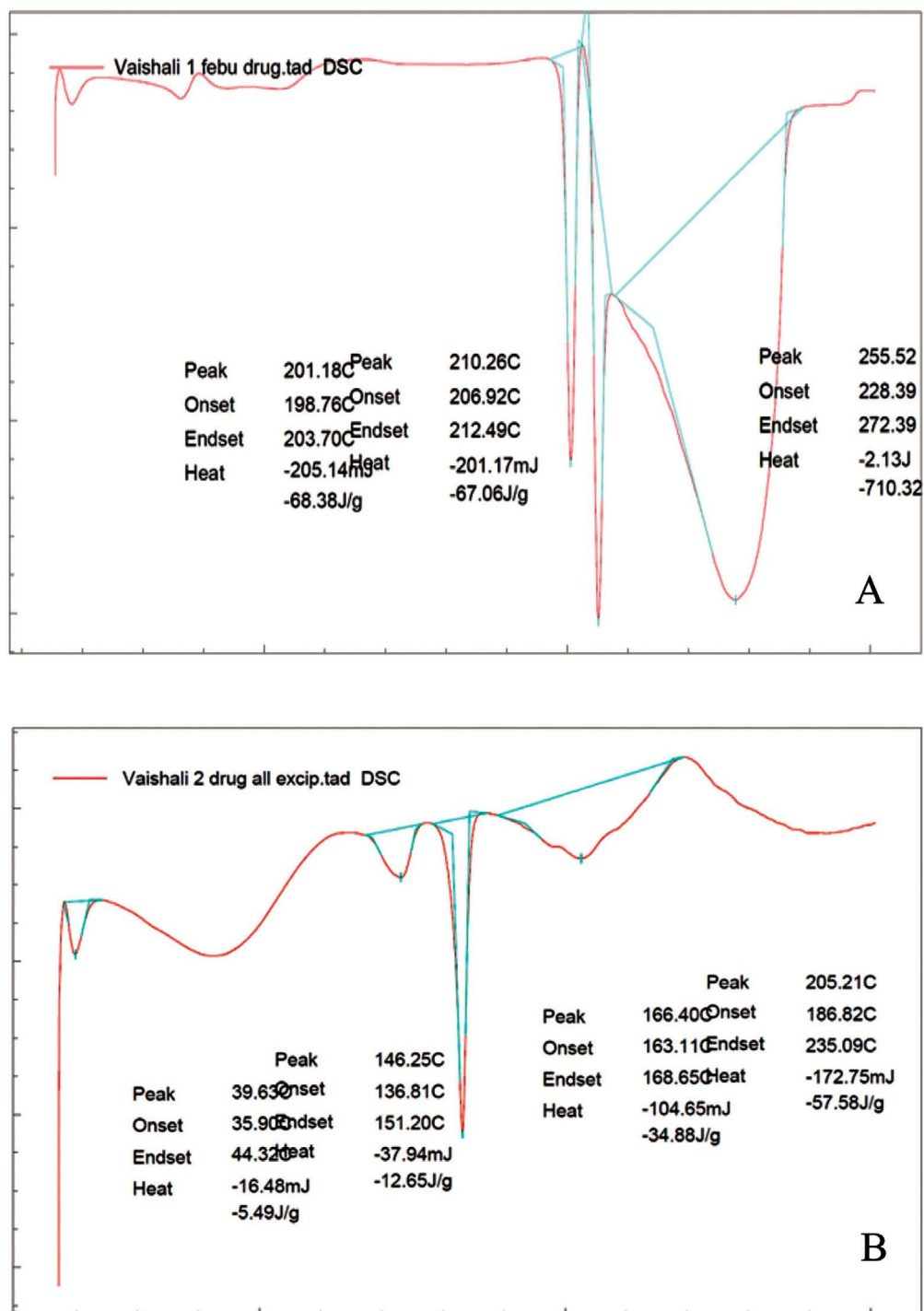


Figure 2. Thermogram of febusostat (A); febusostat and polymers (B).

physical mixture and pure drug all solid dispersion prepared by any one of three methods shows greater saturation solubility (Fig. 5). When we compare the effectiveness of polymer, the Kolliphor P237 shows greater in solubility enhancement than Kolliphor P188 and Eudragit RLPO irrespective of solid dispersion techniques. While comparing the solid dispersion techniques, the spray drying technique was more effective as it shows higher saturation solubility than hot melt (fusion) technique and solvent evaporation technique. This may be due to free flowing,

spherical and porous solid dispersion produced by spray drying technique.²⁷ If we compare the drug to polymer ratio, the 1:2 was found to be highly effective as it shows higher saturation solubility than 1:1 and 1:1.5 ratios irrespective of solid dispersion techniques. Thus, Kolliphor P237 with 1:2 drug-to-polymer ratio using spray drying technique gives superior solid dispersion which has high saturation solubility (0.632 mg/ml, 44-fold, FSD24).

As per “ICH Q3C (R6) Impurities: Guideline for Residual Solvents” acetone is described as a Class 3 solvent.²⁸

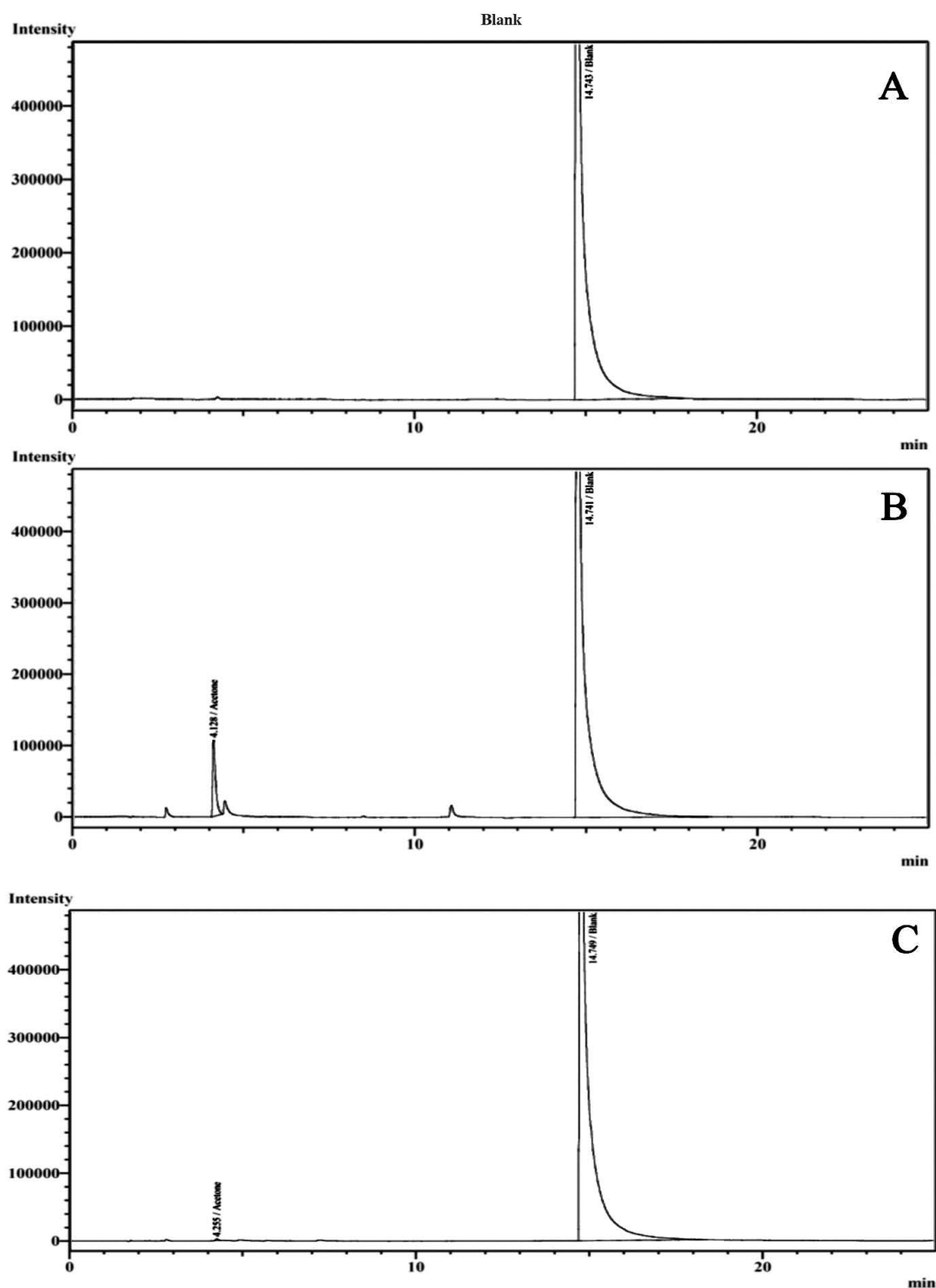


Figure 3. Gas chromatograph of blank sample (A); standard sample (B), and test sample (FSD24) (C).

This is a solvent with low toxic potential and therefore, the concentration of acetone is limited up to 5000 ppm or 0.5% in a drug product. In the current study, evaporation of acetone was maintained during spray drying, effectively. As per **Table 4**, concentration of acetone was lower than 82.7 ppm in the developed febuxostat solid dispersion (FSD24), therefore drug product is accepted as suitable in terms of residual solvent content and related toxicity. The chromatograms for above data are shown in **Fig. 3**.

$$\text{Acetone (ppm)} = \frac{10776.7}{1646373.7} \times \frac{0.635}{100} \times \frac{0.79}{1} \times \frac{0.1}{5} \times \frac{5}{0.10057} \times \frac{99.5}{100} \times 1000000$$

$$\text{Acetone} = 82.7 \text{ ppm (Limit NMT 5000 ppm)}$$

Scanning electron microscopy was performed for best batch from each solid dispersion technique batches which having highest saturation solubility viz. hot melt technique (FSD 6), solvent evaporation (FSD 15), spray drying (FSD

24) and physical mixture of febuxostat and polymer (FSD 33) which is shown in **Fig. 4**.

Untreated pure FXT drug powder and optimized batch FXT solid dispersion (FSD24) showed essentially similar diffraction pattern and lattice spacing, suggesting that the prepared solid dispersion did not undergo gross structural modification. The X-ray diffraction (XRD) scan of untreated FXT showed intense peaks of crystallinity, whereas the XRD pattern of the FXT (FSD24) exhibited halo pattern with less intense and denser peaks compared to pure FXT indicating the decrease in crystallinity or partial amorphization of the drug in its solid dispersion form (**Fig. 6**). As shown in **Table 5**, the crystallinity for untreated pure FXT drug powder and optimized batch FXT solid dispersion (FSD24) were found to be 92.01 and 34.56, respectively. The relative degree of crystallinity was found to be 0.376. This result suggests amorphization of the drug in its solid dispersion form. Hence, improved drug dissolution is expected from formulated optimized batch.

CONCLUSIONS

Kolliphor P237 (1:2 ratio) was optimized as sustained release hydrophobic polymer and it has successfully incorporated the drug in its polymer matrix via spray drying process which showed excellent increase in the solubility and amorphous powder characteristics. The percentage yield was very good for the solid dispersion obtained by hot melt method. DSC, XRD and SEM which revealed decreased crystallinity and improved amorphous form of drug due to drug polymer interaction. Various dosage forms can be prepared by reducing particle size (increase in solubility) using amorphous solid dispersion of the drug. Taking the advantage of a shorter half-life of febuxostat drug, its release can be sustained by combining it with various hydrophilic and hydrophobic polymers. Our study results will help to formulate various solid dosage forms using Kolliphor P237 polymer to enhance drug entrapment efficiency as well as solubility of the drug.

Table 3. Saturation solubility results of solid dispersions prepared by hot melt, solvent evaporation, spray drying method and physical mixture

Batch No.	Saturation solubility		Batch No.	Saturation solubility		Batch No.	Saturation solubility		Batch No.	Saturation solubility	
	mg/ml	Fold		mg/ml	Fold		mg/ml	Fold		mg/ml	Fold
Pure drug	0.0139	1	Pure drug	0.0139	1	Pure drug	0.0139	1	Pure drug	0.0139	1
FSD1	0.251	18.05	FSD10	0.176	12.64	FSD19	0.401	28.86	FSD28	0.034	2.48
FSD2	0.279	20.05	FSD11	0.209	15.00	FSD20	0.530	38.16	FSD29	0.040	2.90
FSD3	0.297	21.40	FSD12	0.219	15.76	FSD21	0.574	41.28	FSD30	0.042	3.03
FSD4	0.277	19.95	FSD13	0.207	14.88	FSD22	0.454	32.63	FSD31	0.041	2.97
FSD5	0.329	23.65	FSD14	0.243	17.48	FSD23	0.521	37.51	FSD32	0.049	3.53
FSD6	0.398	28.65	FSD15	0.292	21.04	FSD24	0.632	45.44	FSD33	0.057	4.11
FSD7	0.174	12.50	FSD16	0.131	9.40	FSD25	0.342	24.57	FSD34	0.026	1.88
FSD8	0.192	13.80	FSD17	0.142	10.20	FSD26	0.399	28.73	FSD35	0.028	2.01
FSD9	0.200	14.40	FSD18	0.146	10.52	FSD27	0.477	34.32	FSD36	0.018	2.00

Table 4. Results of residual solvent analysis

Peak parameters	Blank	Standard		Test (FSD24)	
	Peak 1	Peak 1	Peak 2	Peak 1	Peak 2
Ret. Time	14.743	4.128	14.741	4.255	14.749
Area	20102268.6	646373.7	17124430.6	10776.7	19242659
Height	2882847	107114	2360758	2292	2588257
Area %	100	3.64	96.36	0.06	99.94

Table 5. Results of XRD analysis for pure drug FXT and optimized formulation

	Area of crystalline peaks	Area of all peaks	Degree of crystallinity	Relative degree of crystallinity
Pure Drug (FXT)	1350.80	1468.11	92.01	0.376
FSD24	229.13	662.90	34.56	

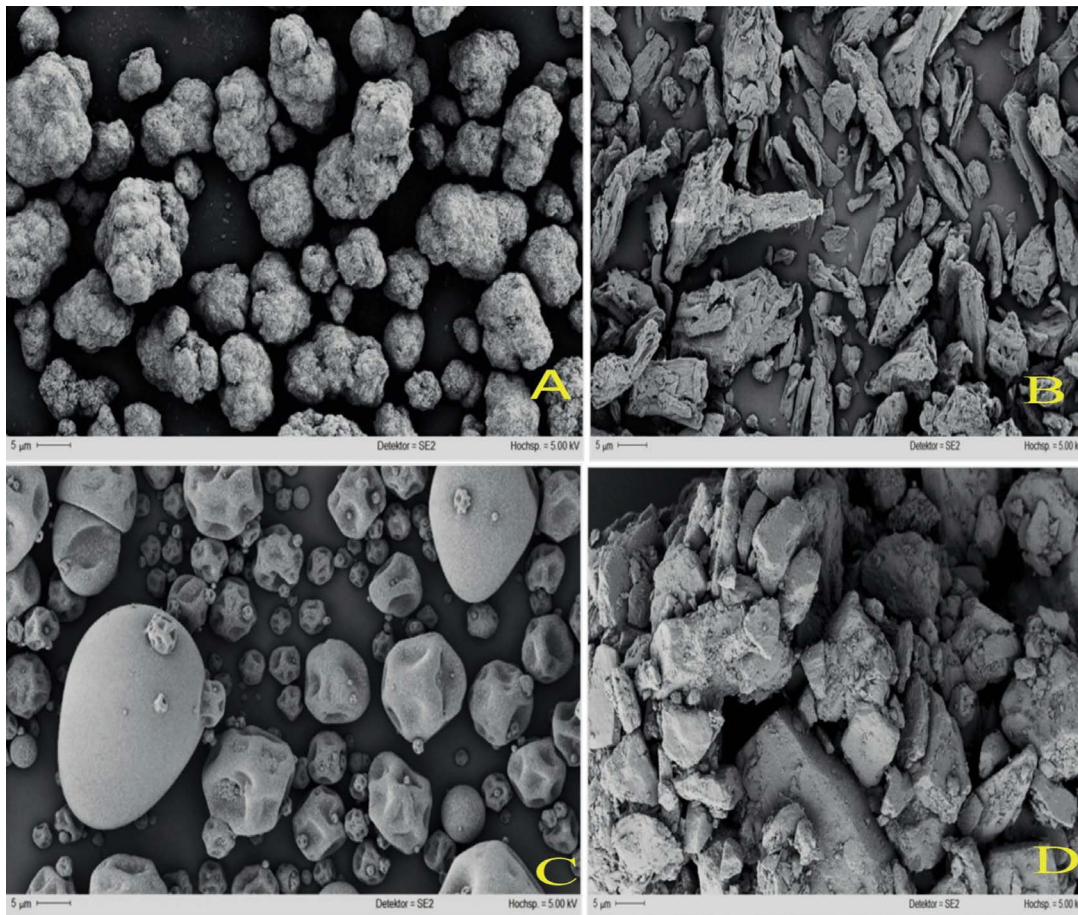


Figure 4. SEM image of febuxostat SD obtained by hot melt technique (FSD 6) (A); SEM image of febuxostat SD obtained by solvent evaporation (FSD 15) (B); SEM image of febuxostat SD obtained by spray drying (FSD 24) (C); SEM image of physical mixture of febuxostat and polymer (FSD 33) (D).

Comparison of Saturation Solubility study of all batches (FSD1 - FSD36) (mg/mL)

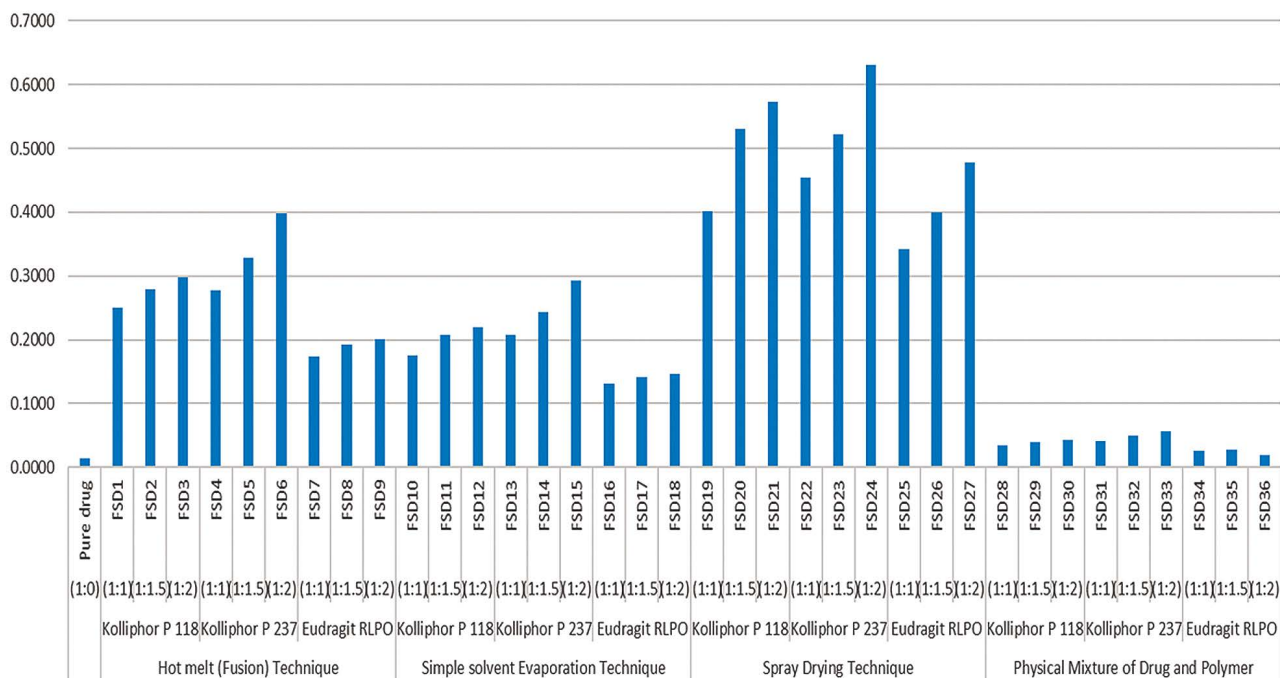


Figure 5. Comparison of saturation solubility study of all batches FSD1 - FSD36.

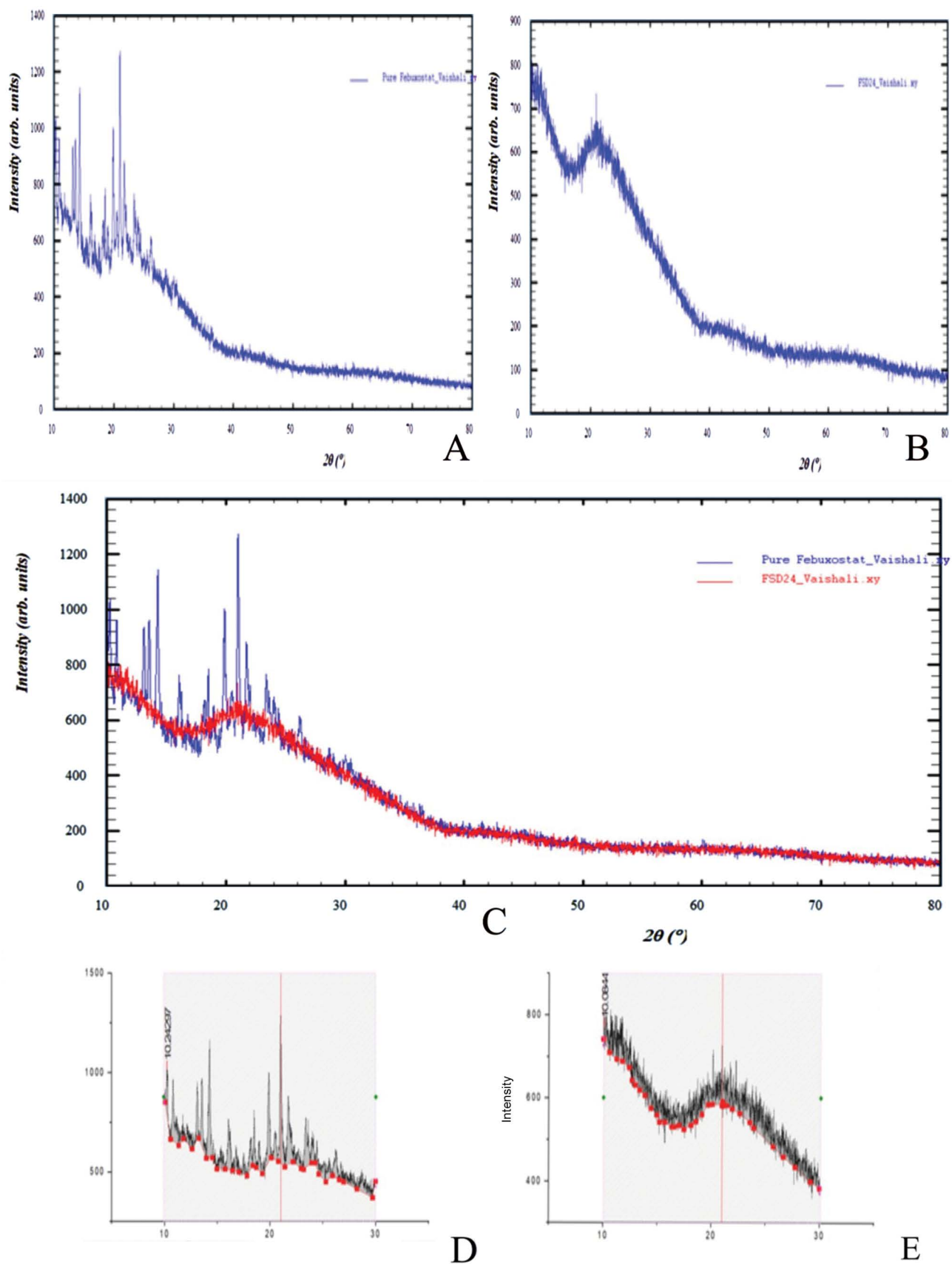


Figure 6. XRD analysis for pure drug febuxostat and optimized formulation (FSD24): XRD plot for pure FXT (A); XRD plot for FSD24 (B); Overlay XRD Plot for optimized batch (FSD24) and pure drug (C); Crystallinity calculation for pure drug FXT (D) and FSD24 (E) using OriginPro 2018 software using OriginPro 2018 software (E).

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Оптимизация методов диспергирования аморфных твёрдых частиц для повышения растворимости фебуксостата

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Резюме

Фебуксостат является селективным ингибитором ксантиноксидазы и относится к группе препаратов класса II BCS с низкой растворимостью и высокой проницаемостью. Растворимость – важнейший параметр, напрямую влияющий на растворение, абсорбцию и биодоступность лекарств. Существуют различные методы, с помощью которых мы можем улучшить растворимость и скорость растворения лекарств с низкой растворимостью. Твердоаморфная дисперсия – один из методов, который может улучшить растворимость, а также характеристики порошка.

Целью настоящего исследования было разработать и оптимизировать различные методы приготовления твёрдой дисперсии с использованием различных пропорций лекарственного средства-полимера и определить партию, которая имеет более высокую растворимость, а также аморфный порошок лекарственного препарата фебуксостат. Для оптимизации были выбраны различные методы, такие как метод горячего расплава, метод испарения растворителя и метод распылительной сушки. Были предприняты попытки улучшить растворимость фебуксостата с использованием лекарственного средства-полимера Kolliphor P 188, Kolliphor P 237, Eudragit RLPO в различных пропорциях (1:1, 1:1,5, 1:2) в качестве носителя. Приготовленную твёрдую дисперсию тестировали на растворимость при насыщении, процент количества, полученного с помощью дифференциальной сканирующей калориметрии (DSC), сканирующей электронной микроскопии (SEM), порошковой рентгеновской дифрактометрии (PXRD) и определения остаточного растворителя. Характеристики твёрдого состояния показали, что фебуксостат присутствует в аморфной форме после смешивания с полимерным носителем. В отличие от чистой формы препарата его твёрдая дисперсия показала лучшую растворимость и аморфные характеристики, что может быть связано с пониженной кристалличностью из-за гидротрофии. Таким образом, метод аморфной твёрдой дисперсии может быть успешно использован для улучшения растворимости, скорости растворения и биодоступности фебуксостата.

Ключевые слова

фебуксостат, Kolliphor P237, твёрдая дисперсия, растворимость, метод распылительной сушки