INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Research Article

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION CHARACTERISTICS OF FENOFIBRATE BY SOLID DISPERSION TECHNIQUE

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Article Received on: 11/09/18 Approved for publication: 12/10/18

DOI: 10.7897/2230-8407.0910242

ABSTRACT

The solubility/dissolution behavior of a drug is key factor influencing its oral bioavailability, being the rate-limiting step for absorption of drugs from the gastrointestinal tract. For effective pharmacological action, aqueous solubility is the most important criteria for prompt dissolution and good absorption. The present study was aimed to enhance the solubility of poorly water soluble drug (BCS Class II) Fenofibrate individually using water soluble polymers like Poly ethylene glycol (PEG 6000) (fusion method) and Poly vinyl pyrrolidone (PVP K30) (solvent evaporation method) in various ratios like 1:1, 1:2, 1:3 and 1:4 separately. Initially, pre-formulation studies like drug excipient compatibility studies by FTIR, DSC and determination of saturation solubility of drug individually in various media like distilled water, 0.1N hydrochloric acid and pH 7.4 phosphate buffer. The formulated solid dispersions were evaluated for percentage yield, drug content and *in vitro* dissolution studies. From the results of pre-formulation studies it was revealed that there was no interaction between drug and excipients and the pure drug was poorly soluble in water. The percentage yield of all formulations was in the range of 60-96 % and drug content was in the range of 56-82 mg. The solid dispersion containing polyvinyl pyrrolidone K 30 in 1:4 ratio showed highest amount of drug release at the end of 30 minutes than other formulations. Finally it was concluded that solid dispersion prepared with PVP K-30 in 1:4 ratio by solvent evaporation method was more soluble than by fusion method.

Keywords: Fenofibrate, Solubility, Dissolution, Solid dispersion, Solvent evaporation method, Phosphate buffer.

INTRODUCTION

The solubility/dissolution behavior of a drug is key factor influencing its oral bioavailability, being the rate-limiting step for absorption of drugs from the gastrointestinal tract. Consequently poor solubility results in low bioavailability increase in the dose, large inter- and intra-subject variation and large variations in plasma drug concentrations under fed versus fasted conditions.[1,2] The property of a solid or liquid or gaseous material known as a solute to be dissolved in a solid or liquid or gaseous solvent to produce a uniform solution is called as Solubility. The type of solvent used and, on the temperature, and pressure used are the chief determinants of solubility of a substance.

The term saturation concentration is defined as the complete solubility of a substance in a given solvent, i.e when more amount of solute is added to the solvent, it does not increase the concentration of the solution.

Here generally liquid which may be a pure substance or a mixture of two liquids could be used as solvent. Solid solution may also be a part but solution in a gas is unusual. Solubility ranges from completely soluble to poorly soluble. Poorly soluble compounds are frequently termed as insoluble.[3]

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

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

Solid Dispersion

Solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous[6]. Solid dispersion systems in which the drug is dispersed in solid water-soluble matrices either molecularly or as fine particles have also shown promising result in increasing bioavailability of poorly water-soluble drugs[7].

MATERIALS AND METHODS

Fenofibrate gift sample was obtained from Cipla, Bangalore, Poly ethylene glycol from Borenpharm Co., Ltd, Povidone from Sigma-Aldrich, Ethanol from Changshu Hongsheng fine chemicals Co., Ltd., Potassium dihydrogen phosphate from Merck Specialties Private Limited, Sodium hydroxide from LOBAL Chemie Laboratory Reagents & Fine Chemicals.

PREPARATION OF PH 7.4 PHOSPHATE BUFFER[8]

Potassium dihydrogen phosphate, 0.2N
About 28.2 g of potassium dihydrogen phosphate was dissolved in small amount of water and then diluted to 1000 ml with water.

Sodium hydroxide, 0.2N
About 8 g of sodium hydroxide was dissolved in small amount of water and then diluted to 1000 ml with water.

pH 7.4 Phosphate buffer
About 50 ml of 0.2N potassium dihydrogen phosphate was taken in a 200 ml volumetric flask. To this 39.1ml of 0.2N sodium hydroxide solution was added and diluted to 200 ml with water.

DETERMINATION OF λMAX FOR FENOFIBRATE IN PH 7.4 PHOSPHATE BUFFER

About 100 mg of Fenofibrate was accurately weighed into 100 ml volumetric flask. Volume is made upto 100 ml using pH 7.4 phosphate buffer after dissolving fenofibtate completely. 20 ml was pipetted out from the above solution and diluted to 100 ml using pH 7.4phosphate buffer. The solution was diluted suitably and scanned in the range of 200-400 nm using UV Spectrophotometer with pH 7.4 phosphate buffer as blank. From the spectrum obtained, the λmax for Fenofibrate was found to be 286 nm in pH 7.4 phosphate buffer.

STANDARD GRAPH FOR FENOFIBRATE IN PH 7.4 PHOSPHATE BUFFER

About 100 mg of Fenofibrate was accurately weighed into 100 ml volumetric flask. Volume is made upto 100 ml using pH 7.4 phosphate buffer after dissolving fenofibrate completely. This is primary stock solution and from this primary stock solution, 10 ml was withdrawn and made upto 100 ml with pH 7.4 phosphate buffer. This is called secondary stock solution. From the above solution, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 ml was withdrawn and made upto 10 ml with pH 7.4 phosphate buffer separately to produce 10 to 100 µg/ml concentrations respectively. Using UV spectrophotometer the absorbances of these diluted solutions were measured at λmax of 286 nm with pH 7.4 phosphate buffer as blank. Standard graph of the fenofibrate was plotted with concentration (µg/ml) in x-axis and absorbance at 286 nm in y-axis is shown in table 1 and figure 1. The concentrations and its absorbances were subjected to linear regression analysis and the regression equation was found to be y = 0.007x - 0.045 and correlation coefficient (r^2) was found to be 0.990.

DETERMINATION OF λMAX FOR FENOFIBRATE IN DISTILLED WATER

About 100 mg of Fenofibrate was accurately weighed into 100 ml volumetric flask and dissolved in small amount of ethanol, made up to 100 ml using distilled water. 20 ml from above solution was pipette out, diluted to 100 ml using distilled water. The above solution was diluted suitably and scanned in the range of 200-400 nm using UV Spectrophotometer with distilled water as blank. From the spectrum obtained, the λmax for Fenofibrate was found to be 286 nm in distilled water.

STANDARD GRAPH FOR FENOFIBRATE IN DISTILLED WATER

About 100 mg of Fenofibrate was accurately weighed into 100 ml volumetric flask and dissolved in small amount of ethanol, made up to 100 ml using distilled water. This is primary stock solution and from this primary stock solution, 10 ml was withdrawn and made upto 100 ml with distilled water. This is called secondary stock solution. From the above solution, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 ml was withdrawn and made upto 10 ml with distilled water separately to produce 10 to 100 µg/ml concentrations respectively. Using UV spectrophotometer the absorbances of these diluted solutions were measured at λmax of 286 nm with distilled water as blank. Standard graph of the fenofibrate was plotted with concentration (µg/ml) in x-axis and absorbance at 286 nm in y-axis is shown in table 2 and figure 2. The concentrations and its absorbances were subjected to linear regression analysis and the regression equation was found to be y = 0.010x - 0.022 and correlation coefficient (r^2) was found to be 0.992.

PRE FORMULATION STUDIES

A) DRUG EXCIPIENT COMPATIBILITY STUDIES
FTIR STUDY[9]
For all the formulations and Fenofibrate the pellets have been prepared using potassium bromide for FT-IR study. The pellets were subjected to FT-IR instrument 'Perkin Elmer FTIR spectrometer, spectrum 1000 Germany' for the collection of IR spectra which are illustrated in figure

Differential Scanning Colorimeter (DSC) studies[10]
Differential scanning calorimetry was done by using Differential scanning calorimeter 'PerkinElmer' to obtain the thermograms. Sample after weighing accurately were placed in an aluminium pan and another empty aluminium pan was used as reference. The scanning was done under nitrogen flow at a scanning rate 10^0C/min in range of 30-450^{0}C. Thermograms were obtained for pure drug, Fenofibrate, Poly ethylene glycol (PEG) 6000 and Polyvinyl pyrrolidone (PVP) K 30 alone and also for combinations of pure drug with polymer in 1:1 ratio individually. The results are shown in figure 3 to 6.

B) DETERMINATION OF SATURATION SOLUBILITY[10]
Using agitation method, the Solubility study was performed and saturated solution of Fenofibrate was prepared using distilled water and pH 7.4 phosphate buffer and it was stirred for 24 hours. The solution filtered through whatmann filter paper 0.45 µm after centrifuging for 15 min over 10,000 rpm. The concentration of Fenofibrate was determined using UV-visible spectrophotometer against respective solvent as blank at λmax of 286 nm. The results are shown in table 4.

DEVELOPMENT OF SOLID DISPERSION[10]
By fusion method
Solid dispersion of Fenofibrate and PEG 6000 prepared in four different weight ratios (1:1, 1:2, 1:3 and 1:4) and denoted as F1, F2, F3 and F4, respectively. With constant stirring Fenofibrate was added to molten PEG and resulting homogenous dispersion was allowed to solidify. The solid dispersion thus formed was ground in mortar and sieved to produce uniform particle size dispersion. Formulation codes are shown in table 3.

By solvent evaporation method
Solid dispersion of Fenofibrate and PVP K-30 were prepared in four different weight ratios (1:1, 1:2, 1:3 and 1:4) and denoted as F5, F6, F7 and F8, respectively. Required quantity of PVP K-30 was dissolved in ethanol and to this Fenofibrate was added. The resulting solution was then homogenized thoroughly and evaporated the solvent. Complete removal of solvent was achieved by drying the mass obtained in oven at 40°C for 24 h. The produced Solid dispersion was then ground, sieved and kept for further analysis. Formulation codes are shown in table 3.

CHARACTERIZATION OF SOLID DISPERSION[10]

Determination of percentage yield
Percentage yield was calculated for each batches of solid dispersion with respect to theoretical yield and practical yield. The results are shown in table 5.

Percentage yield = (Practical yield / Theoretical yield) x 100

Estimation of drug content in solid dispersion
Sample containing 50mg of prepared solid dispersion was accurately weighed and dissolved in freshly phosphate buffer pH

7.4 in a 100 ml volumetric flask .The volume was made up to 100 ml with phosphate buffer pH 7.4. The absorbance of the resulting solution was measured at 286 nm for Fenofibrate, against blank (phosphate buffer pH 7.4) using UV spectrophotometer. The results are shown in table 5.

***In vitro* dissolution rate studies on solid dispersions**

The *In vitro* dissolution for the prepared solid dispersions was performed using Labindia Disso 2000 dissolution test apparatus. Solid dispersions equivalent to 100 mg of Fenofibrate were filled in empty hard gelatin capsules were placed in 900ml of pH 7.4 phosphate buffer as dissolution medium. The speed was maintained at 50 rpm using paddle for 30 minutes. The temperature of the dissolution medium was maintained constant at 37±0.5^{0}C throughout the study. Samples of about 10 ml were pipette out at regular time intervals at 10, 20 and 30 min. The sink condition was maintained by replacing with an equal volume of fresh dissolution medium. The withdrawn aliquots were filtered through whatmann filter paper 0.45 µ, suitably diluted and assayed for Fenofibrate at 286 nm using UV spectrophotometer. The dissolution experiments were conducted in triplicate. The results are shown in table 6 and figure 7.

Table 1: Standard curve of Fenofibrate in pH 7.4 phosphate buffer

S.No	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.066
3	20	0.116
4	30	0.176
5	40	0.238
6	50	0.311
7	60	0.385
8	70	0.465
9	80	0.555
10	90	0.663
11	100	0.733

Table 2: Standard curve of Fenofibrate in distilled water

S.No	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.078
3	20	0.192
4	30	0.214
5	40	0.364
6	50	0.510
7	60	0.684
8	70	0.761
9	80	0.827
10	90	0.935
11	100	1.027

Table 3: Formula for the preparation of solid dispersion of Fenofibrate with different polymers

Formulation code	Formulation	Carrier	Drug : carrier	Method
F1	Solid Dispersion	PEG 6000	1:1	Fusion method
F2			1:2	
F3			1:3	
F4			1:4	
F5	Solid Dispersion	PVP K 30	1:1	Solvent evaporation
F6			1:2	
F7			1:3	
F8			1:4	

Table 4: Saturation solubility of Fenofibrate in various medias

Name of the media	Saturation solubility of drug (in mg/ml)
Distilled water	0.69
pH 1.2 buffer	0.77
pH 7.4 phosphate buffer	25.57
Ethanol	36.40

Table 5: Characterization of solid dispersion of Fenofibrate

Formulation Code	Percentage yield (% w/w)	Drug content (mg)
F1	60	56
F2	65	57
F3	66	57
F4	70	58
F5	70	61
F6	75	74
F7	75	78
F8	96	82

Table 6: *In vitro* dissolution profile for solid dispersions of Fenofibrate

Time (min)	Percentage of drug released (%)							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
10	16.24	18.82	18.27	15.18	12.89	18.62	20.58	21.19
20	30.59	32.61	31.67	29.54	28.34	31.63	37.18	39.24
30	45.64	46.41	46.80	47.31	47.44	52.59	53.49	56.06

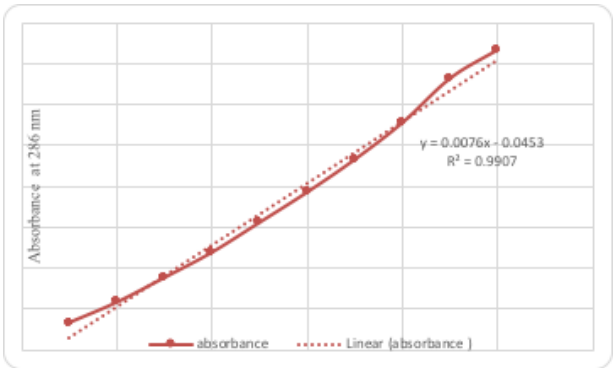

Figure 1: Standard curve of Fenofibrate in pH 7.4 phosphate buffer

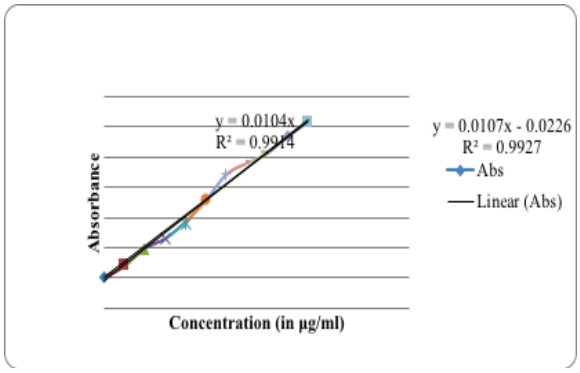

Figure 2: Standard curve of Fenofibrate in distilled water

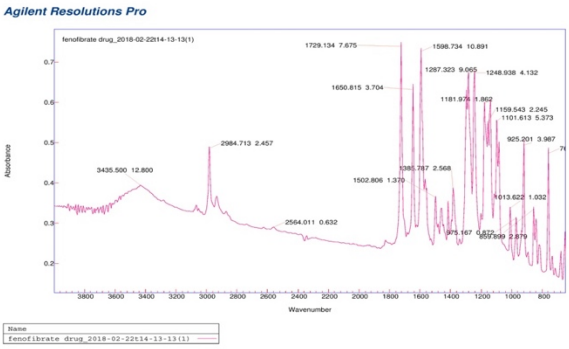

Figure 3: FTIR for Fenofibrate

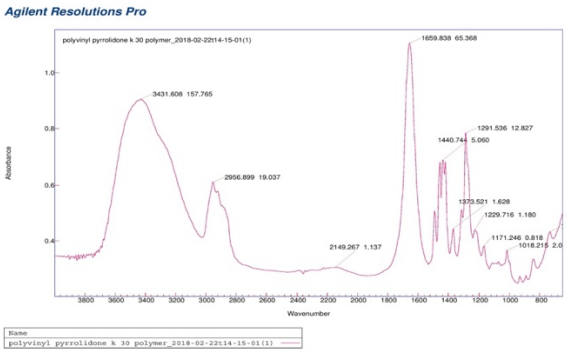

Figure 4: FTIR for Povidone

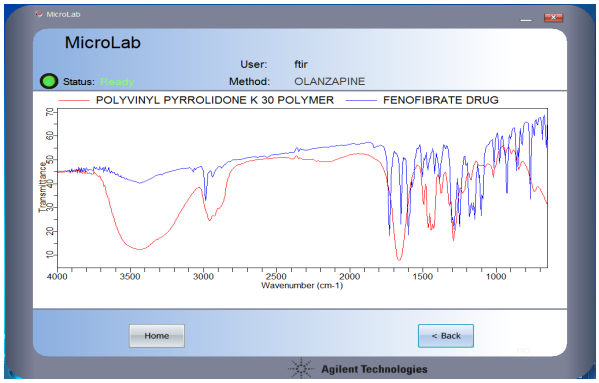

Figure 5: FTIR for Fenofibrate with Povidone

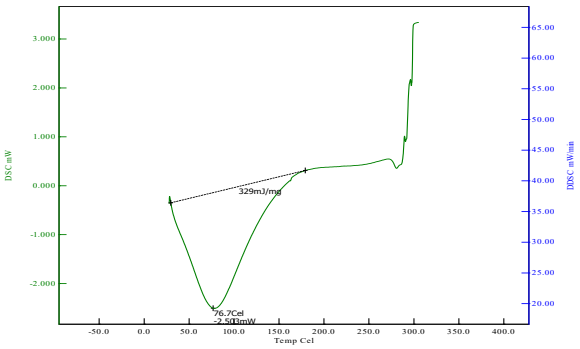

Figure 6: DSC Thermogram for Fenofibrate

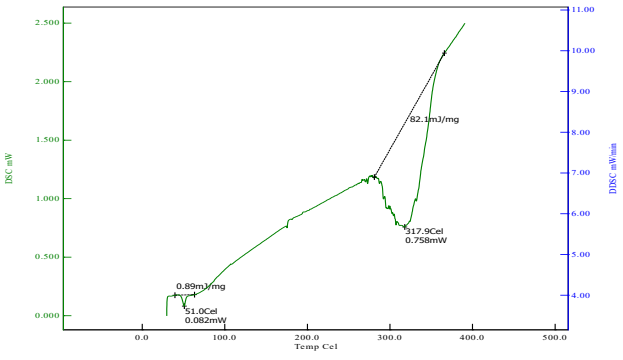

Figure 7: DSC Thermogram for Fenofibrate with polymer in 1:1 ratio

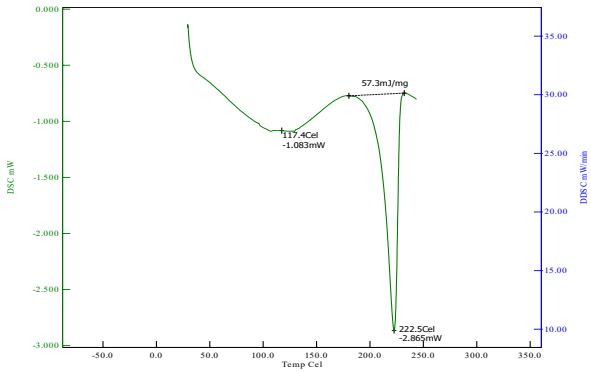

Figure 8: DSC thermogram for PEG 6000

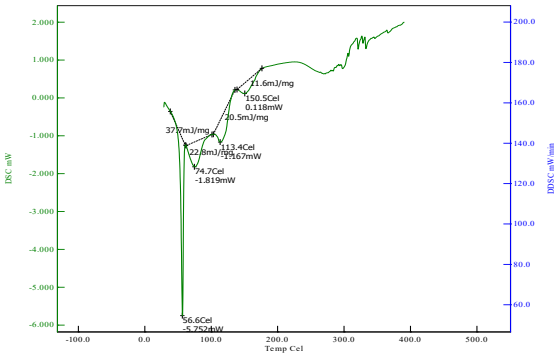

Figure 9: DSC thermogram for Povidone

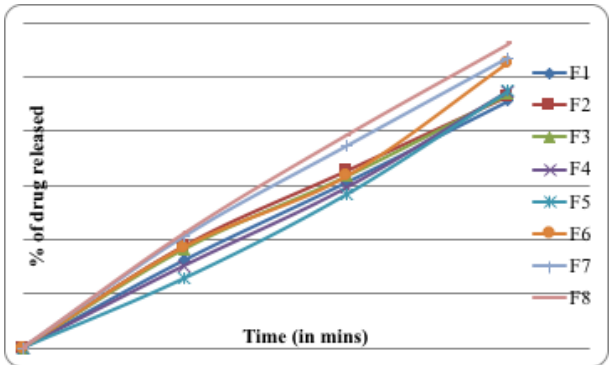

Figure 10: *In vitro* dissolution profile for solid dispersions of Fenofibrate

RESULTS & DISCUSSION

PRE FORMULATION STUDIES

Drug excipient compatibility studies (FTIR)
The FTIR studies were shown in figure no. 3 to 5. From the results of pre-formulation studies, it was revealed that there no chemical incompatibility between drug and excipients from FTIR studies.

Drug excipient compatibility studies (DSC)
The DSC thermogram shown in figure no. 6 to 9, there was a sharp endotherm peak at 76°C for Fenofibrate which was shifted to 51°C when it is combined with polymer at 1:1 ratio. From the results of pre-formulation studies, it was revealed that there no chemical incompatibility between drug and excipients from DSC studies.

Determination of saturation solubility
The saturation solubility studies is shown in table no. 4. It is found that the solubility of Fenofibrate was higher in ethanol and pH 7.4 phosphate buffer than water and pH 1.2 buffer. So, pH 7.4 phosphate buffer was chosen as dissolution media for *in vitro* dissolution studies.

CHARACTERIZATION OF SOLID DISPERSION

Determination of percentage yield
The percentage yield for various ratios of different drug and polymer were calculated and shown in table no.5. The results revealed that the percentage yield was high in 1:4 ratio solid dispersion prepared by solvent evaporation method than compared to fusion method.

Estimation of drug content in solid dispersion
The drug content for various ratios of different drug and polymer were calculated and shown in table no.5. The results revealed that the drug content was high in 1:4 ratio solid dispersion prepared by solvent evaporation method than compared to fusion method.

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

CONCLUSION

Fenofibrate is a lipid regulating agent which is a fibric acid derivative has low bioavailability when given orally because it is a poorly water soluble drug with a plasma elimination half-life of 20 hours. The present study is aimed to enhance the solubility of Fenofibrate by solid dispersion methods like fusion and solvent evaporation method using hydrophilic polymers poly ethylene glycol 6000 and povidone K30 thereby increasing the bioavailability of the drug. From the results of pre-formulation studies, it was revealed that there no chemical incompatibility between drug and excipients from FTIR and DSC studies. Solubility of Fenofibrate was high in ethanol and pH 7.4 phosphate buffer than water and pH 1.2 buffer, therefore, pH 7.4 was selected as media for further characterization. Solid dispersion of Fenofibrate was formulated with poly ethylene glycol 6000 (fusion method) and povidone K30(solvent evaporation method) in various ratios like 1:1, 1:2, 1:3 and 1:4 separately and compared the results of percentage yield, drug content and percentage drug released at the end of 30 minutes for all formulations and was found to be high in solid dispersion containing polyvinyl pyrrolidone K 30 (PVP K30) in 1:4 ratio than other formulations of PVP K30 and PEG 6000 which may be due to increased entrapment of drug in solvent evaporation method than fusion method.

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Cite this article as:

D. Christopher Vimalson *et al*. Enhancement of solubility and dissolution characteristics of fenofibrate by solid dispersion technique. Int. Res. J. Pharm. 2018;9(10):145-150 http://dx.doi.org/10.7897/2230-8407.0910242

Source of support: Nil, Conflict of interest: None Declared