Current Pharma Research
ISSN: 2230-7842
CPR 1(2), 2011, 127-134.

Dissolution Enhancement of Fenofibrate by Solid Dispersion Technique.

[*1]Patel Tejas, [2]Patel L.D, [1]Adeshara S. P, [1]Patel Timir, [1]Makwana Sunil, [1]Patel Tushar.
[1]faculty of pharmacy, Dharmsinh Desai University, Nadiad, Gujarat, India, [2]C. U. Shah College of Pharmaceutical education and research, Wadhwan City, Gujarat, India.

Abstract
The objective of the present investigation was to improve the solubility and the dissolution rate of Fenofibrate (FNO), a poorly water-soluble drug by solid dispersion technique using a water-soluble carrier, Poloxamer 407 (POL). The layophillization technique was used to prepare solid dispersions. A 3^2 full factorial design approach was used for optimization wherein the amount of Poloxamer 407(mg) (X_1) and the Lyophilization Temperature (^{0}C) (X_2) were selected as independent variables and the $T_{100\%}$ (min) and angle of repose was selected as the dependent variable. Multiple linear regression analysis revealed that for obtaining higher dissolution of FNO from POL solid dispersions, a high amount of Poloxamer 407 and a lower freeze drying temperature of were suitable. The differential scanning calorimetry and x-ray diffraction studies demonstrated that enhanced dissolution of FNO from solid dispersion might be due to a decrease in the crystallinity of FNO in lyophilized POL during solid dispersion preparation. Dissolution enhancement of FNO was obtained by preparing its solid dispersions in POL using layophillization technique. The use of a factorial design approach helped in identifying the critical factors in the preparation and formulation of solid dispersion.

Key Words
Solid dispersion, dissolution enhancement, factorial design, poloxamer 407, fenofibrate.

Introduction
The poorly water-soluble drugs often show an erratic dissolution profile in gastrointestinal fluids, which consequently results in variable oral bioavailability and low absorption rate[1]. To improve the dissolution and bioavailability of poorly soluble drugs, researchers have employed various techniques, such as micronization, solubilization, salt formation, complexation with polymers, change in physical form, use of prodrug and drug derivatization, alteration in pH, addition of surfactants, and others[2,3]. Chiou and Rigelman and Serajuadin et al[4,5] have used the solid dispersion technique for dissolution enhancement of poorly water-soluble drugs. Among the various approaches, the solid dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble active pharmaceutical ingredients because it is simple, economic, and advantageous[6]. Sekiguchi and Obi[7] were the first to propose the solid dispersion method using water-soluble carriers to improve the dissolution characteristics of poorly water-soluble drugs.

***Corresponding Author:**
tejaspatel264@gmail.com

In this method, the drug is thoroughly dispersed in a water-soluble carrier by melting, solvent, or solvent-melting methods[4]. Many water-soluble carriers have been employed for preparation of solid dispersion of poorly soluble drugs. The most common are polyethylene glycols[8,9], polyvinyl pyrrolidone[10,11], lactose[12], β-cyclodextrin[13,14] and hydroxypropyl methylcellulose[15]. Recently, Poloxamer, a group of block copolymer nonionic surfactants, have attracted considerable attention for application in preparation of solid dispersions[16,17,18]. These polymers are widely used as emulsifiers, solubilizing agents, and suspension stabilizers in liquid, oral, topical, and parenteral dosage forms and also act as wetting agents and plasticizers, and have been reported for enhancing the solubility and bioavailability of sparingly soluble drugs in solid dosage forms[19,20]. Nine grades of Poloxamer have been evaluated by Saettone and coworkers[21] as solubilizers for tropicamide, a poorly water-soluble drug. Solubility was found to increase as the oxyethylene content increased. Poloxamer 407 (POL) is a nonionic block copolymer chain and has been used by researchers to increase the aqueous solubility of poorly water-soluble drugs[22, 23, 24]. POL was thus selected as a carrier for dissolution enhancement of a poorly water-soluble drug.

A 3^2 full factorial design approach was used for optimization of process variables on dissolution characteristics. The aim of the present work was to study the joint influence of the independent variables the amount of Poloxamer 407(mg) (X_1) and the Lyophilization Temperature (^{0}C) (X_2) on the dependent variables the $T_{100\%}$ (min) and angle of repose. Physicochemical characterization was performed to evaluate the occurrence of chemical interaction between the drug and carrier molecule.

MATERIALS AND METHODS

Materials

Fenofibrate (99% purity) was obtained from Cadila Pharmaceuticals Ltd, India. Poloxamer 407 (Pluronic F127) was obtained from BASF (Mount Olive, NJ, USA). Sodium hydroxide and polyoxyethylene sorbitan monooleate (Tween 80) were purchased from Sigma (UK). Other excipients used were of analytical grade. All chemicals were used as received.

Preparation of solid dispersions

Poloxamer 407 and Fenofibrate were dissolved in a minimum amount of Chloroform. This solution was rapidly solidified by transferring small portions with a Pasteur pipette onto the inner surface of a cold flask rotating in a -50°C methanol bath. After a certain layer thickness was obtained, the flask was attached to the vacuum adapter of the lyophilizer. The solvent was sublimed under a pressure of 8-10 mmHg and condensed onto a -50^{0}C/-60°C/-70^{0}C condenser. After the solvent was completely removed, the powder residue appeared as a porous, light and fluffy mass. The lyophilized preparations were stored in a dessicator at room temperature. The pulverized mass was sifted through a #120 sieve, weighed, and transferred to amber colored Type-I glass vials, stored at 30^{0}C ± 1^{0}C and the yield was determined using following formula:

$$Yield = \left(\frac{a}{b+c}\right) \times 100,$$

where, a is the weight of the solid dispersion sifted through a #120 sieve, b is the weight of FNO taken for solid dispersion preparation, and c is the weight of POL taken for solid dispersion preparation.

Experimental design

A 3^2 full factorial design was employed to systematically study the joint influence of the effect of independent variables X_1 and X_2 on the dependent variable. In this design, 2 factors are evaluated, each at 3 levels, and experimental trials are performed at all 9 possible combinations. A statistical model incorporating interactive and polynomial terms is used to evaluate the response. Where, Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs, and b_i is the estimated coefficient for the factor X_i. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_{21} and X_{22}) are included to investigate nonlinearity. The composition of the factorial design batches are shown in Table 1. Table 2 shows actual values of independent variables and levels of independent factors.

In- Vitro Dissolution Study

An ELECTROLAB dissolution test apparatus type II (Paddle) at rotation speed of 50 rpm was used for the study. Dissolution of the drug and solid dispersion was carried out on an equivalent of 100 mg of the Fenofibrate in 0.1 M SLS as dissolution media. The volume and temperature of the dissolution media were 900 ml and 37 ± 0.2 0C, respectively. After fixed time intervals, 5 ml of samples were withdrawn and replace the same fresh dissolution media so as to maintain sink condition. The samples were filters through 0.2µm filters and diluted with HPLC mobile phase and these samples were assayed HPLC at 286 nm. To increase the reliability of the observations, the dissolution studies were performed in triplicate.

Differential scanning calorimetry studies

Thermal properties of the untreated drug and the prepared solid dispersion were analyzed by DSC (TA Instruments, USA, and Model: LST 2960). The samples were heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 30 to 350 ^{0}C at a heating rate of 10 ^{0}C/ min, using nitrogen as blanket gas.

FT-IR Studies

FT-IR spectra of prepared Lyophilized solid dispersion were recorded on Shimadzu FT IR – 8400 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400 – 4000 cm^{-1} at spectral resolution of 2 cm^{-2} and ratio

against background interferogram. Spectra were analyzed by software supplied by Shimadzu.

X-ray powder diffraction analysis

Crystallinity of the drug and the samples was determined using the Philips Analytical XRD (Model: PW 3710, Holland) with copper target. The conditions were: 40 kV voltages; 30 mA current; at room temperature. The samples were loaded on to the diffractometer and scanned over a range of 2^{0} values form 10 to 80^{0} at a scan rate of 0.05^{0} /min.

Results and Discussion

In-Vitro Dissolution Studies

Results of in vitro drug release from different formulations of solid dispersions shown in figure 1. In vitro dissolution studies showed Batch F1, F2 and F3 required 150 minutes, 135 minutes and 120 minutes for dissolving 100% drug respectively. It indicated T100% was decreased proportionally on the increasing amount of Polymer. Amount of polymer was in increasing order in batch F4, F5, F6 and F7, F8, F9 similar to F1, F2 and F3 (Table 2). In the comparison of Batch F3, F6 and F9 order of T100% was F9<F6<F3. It indicated as the amount of Poloxamer 407 was increased, T100% was decreased, that was might be due to Poloxamer 407 is high molecular weight hydrophilic polymer which disperse drug at molecular level and convert crystalline Fenofibrate into amorphous form.

Optimization of formulation by full factorial design

A 3^2 full factorial design was employed to systematically study the joint influence of the effect of independent variables X_1 and X_2 on the dependent variable. In this design, 2 factors are evaluated, each at 3 levels, and experimental trials are performed at all 9 possible combinations. A statistical model incorporating interactive and polynomial terms is used to evaluate the response. The computation for optimized formulation was carried using software; DESIGN EXPERT 7.1.6 (STAT-EASE).The response variables considered for optimization were angle of repose and T100%. The optimized formulation was obtained by applying constraints (goals) on dependent (response) and independent variables (factors).

$$T_{100\%} = +93.33 - 44.17 * X_1 + 15.00 * X_2 + 0.000 * X_1 * X_2 - 2.50 * X_1^2 + 0.000 * X_2^2 \text{ ------ (1)}$$

$$\text{Angle of Repose} = +33.49 + 3.34 * X_1 + 8.44 * X_2 + 1.80 * X_1 * X_2 - 1.76 * X_1^2 + 1.15 * X_2^2 \text{ -----(2)}$$

Where, $X_1$and X_2 are the amount of Poloxamer 407 and Lyophilization Temperature respectively.

In Equation (1), A Coefficient of Independent factor X_1 with a negative sign (-44.17 X_1) indicates $T_{100\%}$ was decreased as the amount of Poloxamer 407 was increased (Formulation F2, F5 and F8) similarly a coefficient of Independent factor X_2 with a positive sign (+15.00 X_2) indicates $T_{100\%}$ was decreased as the Lyophilization temperature was decreased (formulation F1, F2, F3, formulation F4, F5, F6 and formulation F7, F8, F9). The coefficients with second order terms (b_{11} and b_{22}) indicate the quadratic nature in which a negative sign indicate (-2.50 X_1^2) as the amount of Poloxamer 407 added in more amount, $T_{100\%}$ decrease (compare formulation F3, F6 and F9) whereas a coefficient with a positive sign (+0.000 X_2^2) indicate as higher Lyophilization temperature, $T_{100\%}$ had to be increase but here it was decrease that may be due to higher Lyophilization temperature increase surface area that assist in dissolution (compare formulation F7, F8 and F9).

The results were impossible in presence of individual Independent factors hence, conclusions cannot be drawn simply by considering the positive or negative mathematical signs of the coefficient of Independent factors (b_1 and b_2) and coefficient of the quadratic term (b_{11} and b_{22}) on the value of $T_{100\%.}$ So combine effect of both of Independent factors are essential to predict and achieving targeted value of $T_{100\%.}$ Positive sign of the interaction term (+0.000) indicated as the both Poloxamer 407 and Lyophilization $T_{100\%}$ decrease (formulation F1, F5 and F9). The magnitude of b_1 (44.17) is greater than b_2 (15) which indicated the greater influence of Poloxamer 407 comparatively Lyophilization temperature on $T_{100\%.}$

Figure 2 shows that $T_{100\ \%}$ was increased as the amount of Poloxamer 407 was increased at the fix value of Lyophilization temperature (-50^{0}C) might be due to hydrophilic nature of Poloxamer 407 which converted crystalline Fenofibrate in to amorphous form. As the Lyophilization temperature decreases, $T_{100\%}$ was decreased at the fix value of Poloxamer 407 (80 mg). Result suggested that presence of Poloxamer 407 and Lyophilization temperature is essential in achieving desired $T_{100\%.}$

The relationship between the dependent and independent variables was further elucidated using

contour plots. Logically it was predefined to obtain the values of the $T_{100\%}$ = 30 minutes for the formulated products. In contour plot only formulation F9 had $T_{100\%}$ near to desired $T_{100\%}$ (Figure 2).

It was arbitrarily decided to obtain the values of the angle of repose less than 30^0 from the formulated products. In Equation (2), A Coefficient of Independent factor A with a positive sign (+3.34 X_1) indicates as the amount of Poloxamer 407 increase, angle of repose increase (Formulation F2, F5 and F8) whereas a coefficient of Independent factor B with a negative sign (+8.44 X_2) indicate as the Lyophilization temperature increase, angle of repose decrease (Formulation F4, F5 and F6). The coefficients with second order terms (b_{11} and b_{22}) indicate the quadratic nature in which a negative sign indicate (-1.76 X_1^2) as the amount of Poloxamer 407 added in more amount, angle of repose had to be decrease but here it was increase that may be due to higher amount of Poloxamer 407 retard powder flow. (formulation F3, F6 and F9) whereas a coefficient with a positive sign (+1.15 X_2^2) indicate as higher amount of Lyophilization temperature, angle of repose had to be increase but here it was decrease that may be due to higher amount of adsorbent make free flow powder (formulation F7, F8 and F9).

The results were never possible in presence of individual Independent factors hence, one cannot draw conclusions by considering the mathematical signs (positive or negative) of the coefficient of Independent factors (b1 and b2) and coefficient of the quadratic term (b_{11} and b_{22}) on the value of angle of repose so combining effect of both of Independent factors was require to predict and achieving targeted value of angle of repose. Positive sign of the interaction term (+ 1.80) indicated as the both Poloxamer 407 and Lyophilization temperature increase, angle of repose decrease (compare formulation F1, F5 and F9). The magnitude of b_2 (8.44) is greater than b_1 (3.34) which indicated the greater influence of Lyophilization temperature comparatively Poloxamer 407 on angle of repose.

Figure 3 showed that as the amount of Poloxamer 407 increase, angle of repose was increase at the fix value of Lyophilization temperature (-50^0C). As the Lyophilization temperature increase, angle of repose was decrease at the fix value of Poloxamer 407 (80 mg).

The relationship between the dependent and independent variables was further elucidated using contour plots. Here, arbitrarily predefined to obtain the values of the angle of repose less than 30 minutes from the formulated products. In contour plot only formulation F9 showed angle of repose near to desired angle of repose (Figure 3). The final selection of the optimized batch would be done after considering the other requirements of the dosage form, i.e.$T_{100\%.}$

FT-IR Studies

The FT-IR spectrum of Fenofibrate, Poloxamer 407, and lyophilized solid dispersion is shown in Figure 4. The characteristic peaks of pure Fenofibrate peaks are observed at 2990, 1740, 1660, and 1600cm $^{-1}$ and observed same in prepared solid dispersion formulation. The Poloxamer 407 exhibits characteristic peaks at 3503, 2884, and 1114 cm^{-1}. IR-spectra of Fenofibrate and solid dispersion are exactly same, and there is no shift of peaks after adsorption of drug onto polymer and surfactants surface; indicating that there is no change in chemical structure of drug after preparing it into lyophilized solid dispersion

Differential scanning calorimetry studies

Figure 5 shows the DSC study of Fenofibrate and Fenofibrate solid dispersions. The corresponding melting point depressions, enthalpy of fusion and degree of crystallinity are shown in figure. A depression in melting point of Fenofibrate was found in solid dispersions, which indicates an interaction of Fenofibrate with carrier molecule Poloxamer 407. The DSC thermograph of Fenofibrate lyophilized formulation shows only endothermic peak; the absence of exothermic re-crystallization peak may be attributed to interaction between drug and polymers.

X-ray powder diffraction analysis

Fenofibrate crystals show various diffraction peaks (figure 6) due to its crystalline structure. However, the lyophilized solid dispersion shows a loss of drug Crystallinity due to drug loading onto polymers and surfactants surface. In optimized lyophilized solid dispersion, a few less intense and wide diffraction peaks of Fenofibrate was observed, which may be attributed to the adsorption process in which some of amorphous drug may have crystallized due to higher temperature. The sharp drug peaks corresponding to drug are absent in the lyophilized solid dispersion. The PXRD patterns of Fenofibrate, Poloxamer 407, and lyophilized solid dispersion showed a total 13,

10, and 22 peaks, respectively. The PXRD of solid dispersion exhibits 17 peaks less than the sum of the number of peaks of Fenofibrate and Poloxamer 407 in their pure forms. This suggests that Crystallinity of both drug and polymer is reduced in the lyophilized solid dispersion. Decrease in Crystallinity of the drug and polymer may contribute to enhancement of dissolution of the drug.

Table 1: Composition of solid dispersions using 3^2 full factorial design.

Formulation Code	Variable levels in coded form	
	X_1	X_2
F1	-1	-1
F2	-1	0
F3	-1	1
F4	0	-1
F5	0	0
F6	0	1
F7	1	-1
F8	1	0
F9	1	1

Table 2: Actual values of Independent Variables & levels

Independent variable	Levels		
	Low	Middle	High
	-1	0	1
X_1: Amount of Poloxamer 407 (mg)	40	80	120
X_2: Lyophilization Temperature(^{0}C)	-30	-50	-70

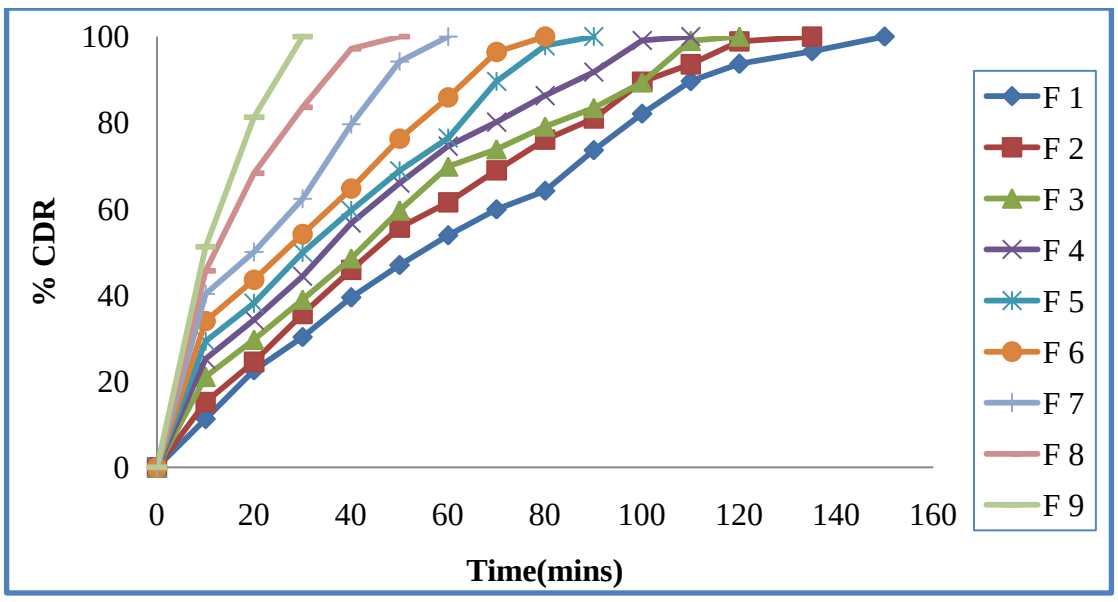

Figure 1: In vitro release profile of different formulation of solid dispersion as per 3^2 full factorial design.

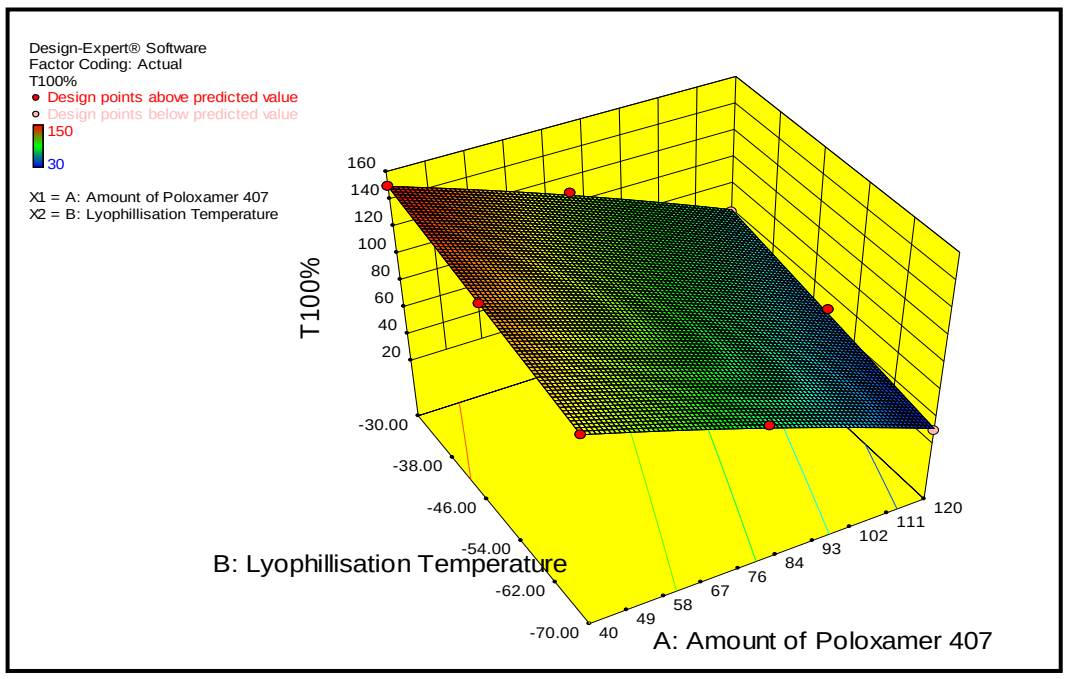

Figure 2: Surface response plot for optimization of T_{100}%.

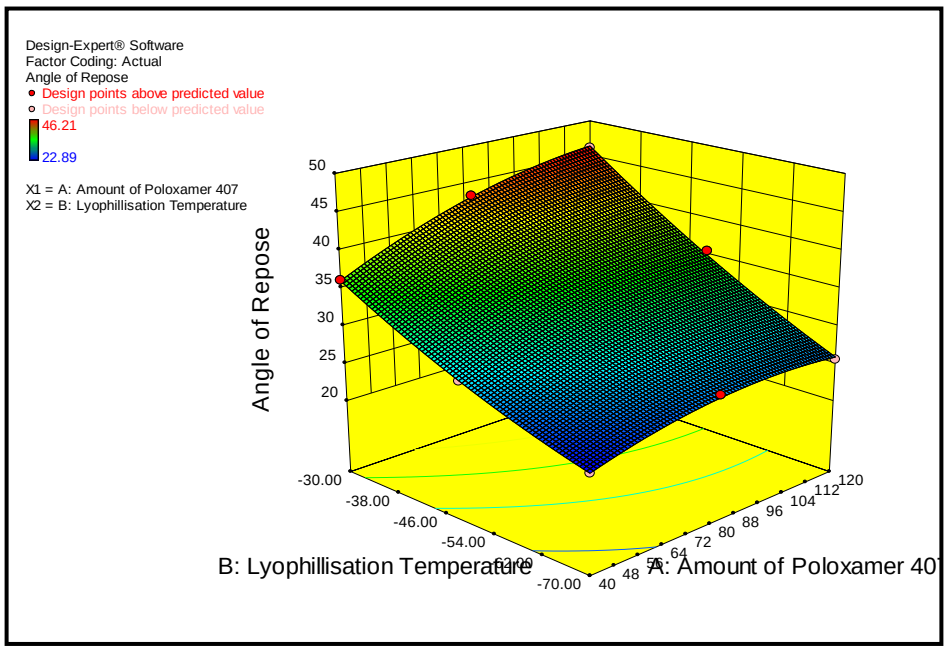

Figure 3: Surface response plot for optimization of Angle of Repose.

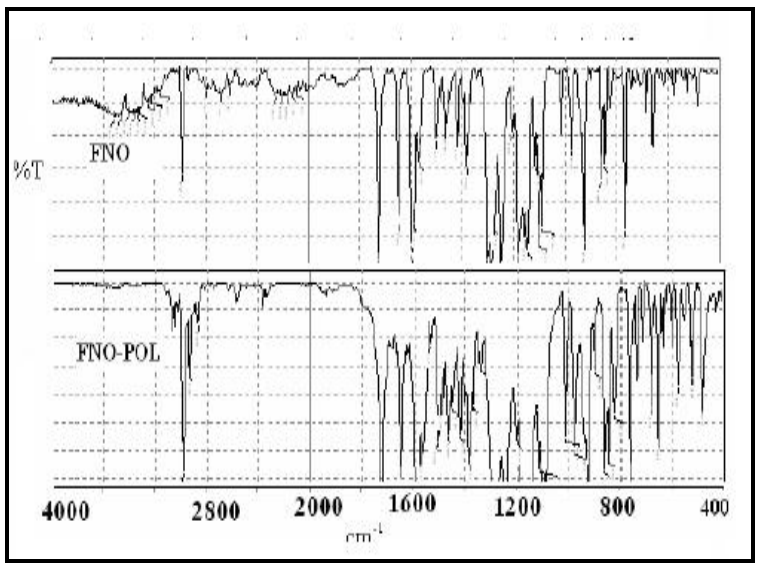

Figure 4: FT-IR spectra of drug alone and Optimized solid dispersion.

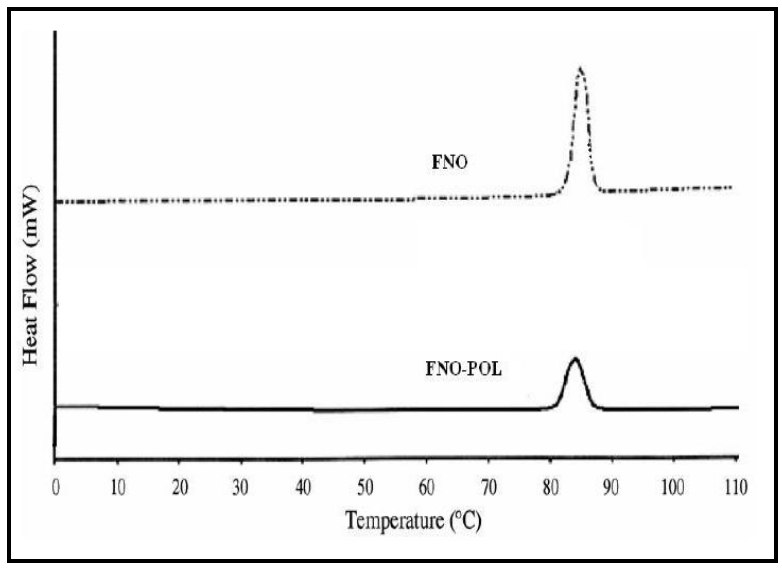

Figure 5: DSC curves of drug alone and Optimized solid dispersion.

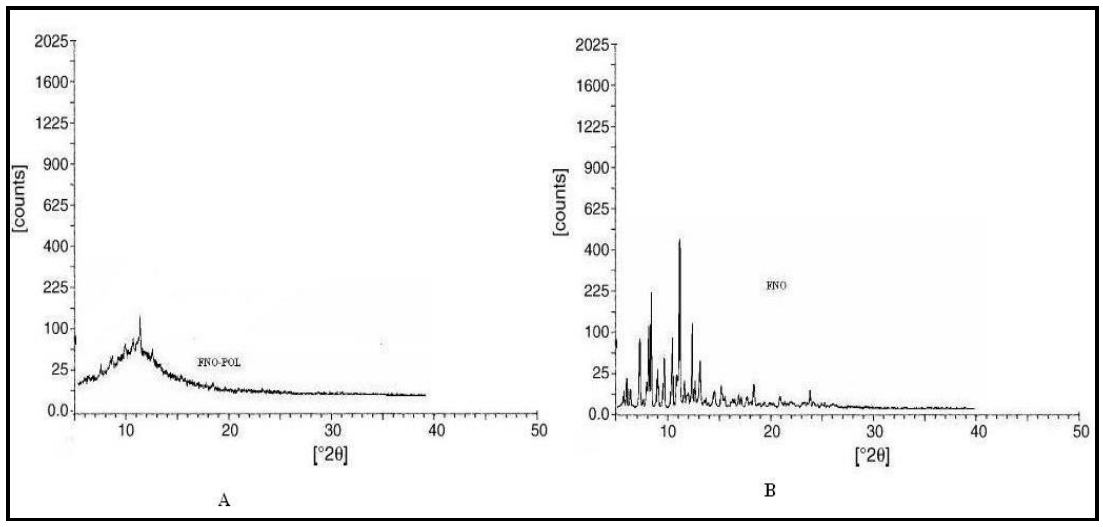

Figure 6: PXRD of Optimized formulation (A) and Pure drug (B).

Conclusions

The results of the experimental study show that the factors amount of Poloxamer 407 (X_1) and Lyophilization temperature (X_2) significantly influences the dependent variable $T_{100\%}$ and Angle of repose. As the Lyophilization temperature was decreased there was increase in amorphous nature of the solid dispersion of drug and due to that there will be increase in solubility of drug and ultimately oral absorption of the drug. Characterization studies revealed that Lyophilization of solid dispersion of Fenofibrate-Poloxamer 407 showed enhancement of Fenofibrate dissolution due to the conversion of Fenofibrate into a less crystalline and/or amorphous form. The application of experimental design techniques for optimization of formulation helps in reaching the optimum point in the shortest time with minimum efforts.

References

1. Munoz JP, Guichard P, Reginault, Micronised fenofibrate. Atherosclerosis 110 (Suppl.), 1994, S45–S48.
2. Hancock BC, Zografi G, Characteristics and significance of the amorphous state in pharmaceutical systems. J. Pharm. Sci. 1997, 86,1–12.
3. Corrigan Ol, Mechanisms of dissolution of fast release solid dispersions. Drug Dev. Ind. Pharm. 1985, 11,697-724.
4. Liversidge GG, Fenofibrate in Britain, H.G. Analytical Profiles of Drug Substances and Excipients. vol. 22, New York: Academic Press, London; 1993, pp. 443–471.
5. Liversidge GG, Cundy KC, Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: absolute oral bioavailability of nanocrystalline danazol in beagle dogs. Int. J. Pharm. 1995, 125,91–97.
6. Adkins JC, Faulds D, Micronised fenofibrate: a review of its pharmacodynamic properties and clinical efficacy in the management of dyslipidemia. Drugs. 1997, 54, 615–633.
7. Guichard JP, Blouquin P, Qing Y, A new formulation of fenofibrate: suprabioavailable tablets. Curr. Med. Res. Opin. 2000, 16, 134–138.
8. Hargrove JT, Maxson WS, Wentz AC, Absorption of oral progesterone is influenced by vehicle and particle size. Am. J. Obstet. Gynecol.1989, 161, 948–951.
9. Jounela P, Pentikainen A, Sothmann, Effect of particle size on the bioavailability of digoxin. Eur. J. Clin. Pharmacol.1975, 8, 365–370.
10. Shakhtshneider TP, Vasiltchenko MA, Politov AA, Boldyrev VV, The mechanochemical preparation of solid disperse systems of ibuprofen–polyethylene Fenofibratecol. Int. J. Pharm.1996, 130, 25–32.
11. Lin YE, Wilken LO, Some effects of a modified lyophilization procedure on dissolution and other properties of digoxin powders and tablets. M.S. Thesis. Auburn University, AL, 1980, p. 63
12. Sugimoto M, Okagaki T, Narisawa S, Koida Y, Nakajima K, Improvement of dissolution characteristics and bioavailability of poorly water-soluble drugs by novel cogrinding method using water soluble-polymer. Int. J. Pharm. 1998, 160, 11–19.
13. Grau MJ, Kayser O, Muller RH, Nanosuspensions of poorly soluble drugs – reproducibility of small scale production, Int. J. Pharm. 2000, 196, 155–157.
14. MacKenzie AP, Principles of freeze-drying Transplant Proc: 8 (Suppl. l), 1976, 181-188.
15. Martindale, the Extra Pharmacopeia 29, Fenofibrate, Pharmaceutical Press: London, 1989, 25.
16. Pikal MJ, Shah S, Senior D, Lang JE, Physical chemistry of freeze-drying: measurement of sublimation rates for frozen aqueous solutions by a microbalance technique. J. Pharm. Sci. 1983, 72, 635-650.
17. Sekiguchi K, Obi N, Studies on absorption of eutectic mixture. 1. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem. Pharm. Bull.1961, 9, 866-872.
18. Sekikawa H, Naganuma T, Fujiwara JE, Nakano M, Arita T, Dissolution behaviors and gastrointestinal absorption of phenytoin in phenytoin-polyvinylpyrrolidone coprecipitate. Chem. Pharm. Bull.1979, 27, 1223-1230.
19. Simonelli AP, Mehta SC, Higuchi WI, Dissolution rates of high energy polyvinylpyrrolidone-sulfathiazole coprecipitates. J. Pharm. Sci.1969, 58, 538-549.

20. Amidon GL, Lennernas H, Shah VP, Crison JR, A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res.1995, 12, 413-420.
21. Garad SD, How to improve the bioavailability of poorly soluble drugs. Am Pharm Rev. 2004, 7.
22. Nokhodchi A, Javadzadeh Y, Reza M, Barzegar JM, The effect of type and concentration of vehicles on the dissolution rates of a poorly water soluble drug (indomethacin) from liquisolid compacts. J Pharm Sci. 2005, 8, 18-25.
23. Chiou WL, Rigelman S, Pharmaceutical application of solid dispersion system. J Pharm Sci. 1971, 60, 1281-1302.
24. Serajuddin A, Solid dispersion of poorly water soluble drugs: early promises, subsequent problems and recent breakthroughs. J Pharm Sci. 1999, 88, 1058-1066.

******