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PREPARATION EVALUATION AND OPTIMIZATION OF FENOFIBRATE SOLID DISPERSION

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ABSTRACT

The term 'solid dispersion' refers to a group of solid products consisting of at least 2 different components, generally a hydrophobic drug and hydrophilic carrier. The solid dispersion technique is useful to reduce particle size from crystalline to micro-crystalline level, which ultimately enhances aqueous solubility of poorly water soluble drugs. The purpose of this study was to develop and evaluate solid dispersions of Fenofibrate for the effective treatment of hypercholesterolemia. Fenofibrateis a BCS class II drug having high lipophilicity and low solubility leads to poor absorption from GIT. The formulations were prepared using Box-Behnken design. In the present work an attempt was made to prepare Fenofibrate solid dispersion by using various surfactants. Surfactants not only enhances the solubility but also improve physical stability of solid dispersion. SLS, Tween 80, Span 80 were used to find efficient surfactant combination and highest drug release. The carriers is essential for development of solid dispersion and polyvinylpyrroli done is used as a carrier for formulating solid dispersion. The optimized formulation showed drug release of 99.55±0.142% at 60 min. The rate of drug release follows zero order kinetics with non-fickian case II transport mechanism. From the study it was concluded that the F4 formulation (Span 80-0.75 ml, Tween 80- 1.5 ml and SLS – 150 mg) showed the optimum result as a solid dispersion for the treatment of hypercholesterolemia.

KEYWORDS: Soliddispersion, Fenofibrate, Surfactants, Zero order release.

1. INTRODUCTION

A poorly water-soluble drug is the one whose dissolution in the gastro intestinal (GI) fluid under ordinary conditions takes a longer time than its transition through the absorption sites in the GI tract. Dissolution in the GI fluid is a critical requirement for a poorly water-soluble drug to be absorbed in the GI tract. When water solubility is less than 1 µg/ml, which is often the case for contemporary drug candidates, the bioavailability from conventional tablet formulations may be unacceptable. With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery presents one of the most frequent and greatest challenges to formulation scientists. The dissolution rate of poorly water soluble drugs from crystalline formulation can be increased by reducing the particle size and increasing surface area.[1] Crystalline drug is in a stable state in the formulated product and will remain in a physically stable state throughout the dissolution phase in the gut lumen. Many physical approaches to improve aqueous solubility include salt formation, particle size reduction, emulsions, micelles, liposome, and macro-/nano particles, but most of the approaches are liquid based which results in problems like instability, in-vivo uncertainty and manufacturing cost.[2] Unlike liquid formulation techniques solid dispersion systems shows significant results in increasing aqueous solubility of poorly water-soluble drug where the drug is dispersed either as fine particles or molecularly in solid water-soluble matrices. The solid dispersion technique is useful to reduce the particle size from crystalline to micro-crystalline level, which ultimately enhances water solubility of poorly water soluble drugs. Because of greatly enhanced surface area obtained in this way the solubility and bioavailability of poorly water soluble drugs were expected to be high. Single or combination of carriers may also be essential for development of solid dispersion.[3][4] Different surfactants are used in solid dispersion to improve solubility of poorly water-soluble drugs. Addition of surfactants not only increases drug-polymer miscibility but also reduces recrystallization. It also improves the wettability of solid dispersion, which leads to increase in dissolution and improved physical stability.[5] In the present work an attempt was made to prepare solid dispersion of Fenofibrate so as to increase its solubility thereby reducing bioavailability problems.

Fenofibrate is a drug of the fibrate class. It is mainly used to reduce cholesterol levels in patients at risk of cardiovascular disease. Like other fibrates, it reduces

both low-density lipoprotein (LDL), very low density lipoprotein (VLDL), and triglyceride level whereas increases high-density lipoprotein (HDL) level.[6] It also appears to have a beneficial effect on the insulin resistance featured by metabolic syndrome. It is used alone or in conjunction with statins in the treatment of hypercholesterolemia and hypertriglyceridemia. So it has been used for many years to lower cholesterol levels and its pharmacokinetic profile is well understood. Fenofibrate belongs to BCS Class II having low solubility (< 0.1 mg/ml) and highly lipophilic (pKa=5.24).[7] Thus the dissolution rate of Fenofibrate is expected to limit its absorption from the gastrointestinal tract.

2. MATERIALS AND METHODS

2.1 Materials

Fenofibrate obtained from YarrowChem, Mumbai, Tween 80 and Span 80 from Burogyne Burdidges & Co.Mumbai, Polyvinylpyrrolidone from Loba chemie, Mumbai and Sodium lauryl sulphate from Isochem laboratories, Kochi.

2.2 Methods

2.2.1 Preformulation studies

Organoleptic properties

Physical appearance of drug was observed and compared with official monograph.

Identification of melting point

Melting point of drug was determined using Melting point apparatus and compared with official monograph.

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 m 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. 1, 2, 3, 4, 5, 6, 7, 8, 9, 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.[6]

- **Solubility studies**

Solubility of Fenofibrate was observed in different solvents such as distilled water, pH 1.2 acetate buffer, pH 7.4 phosphate buffer, ethanol and acetone.

- **Drug-Exicipient Interaction Studies**

In order to find out the possible interactions between Fenofibrate, carrier and surfactants used in formulation of solid dispersion. Fourier Transform Infra-red Spectroscopy (FT-IR) analysis was carried out on pure substances and their physical mixtures.

- **FT-IR** spectra of pure drug, polyvinyl pyrrolidone, tween 80, span 80, SLS and their physical mixtures were taken by KBr pellet technique between 400-4000 cm^{-1}. This is to ensure that no incompatibility between drug and polymers. Once spectra were recorded, the peaks of pure drug and physical mixtures of polymers, drug and surfactants were compared for incompatibility.

2.2.2 Preparation of Fenofibrate solid dispersion

Required quantity of polyvinylpyrrolidone was dissolved in ethanol and to this Fenofibrate was added. Then weighed amount of surfactants were added to the resulting solution. Then homogenized thoroughly and evaporated the solvent at 23-65°C. The produced solid dispersion was then ground, sieved and kept for further analysis. Formulation codes are shown in table no:1

Design Expert Stat Ease Software was used to design formulations. Seventeen formulations with Different concentrations of Span 80, Tween 80 and SLS were suggested by the software. The formulation is shown in table no.1

Table No. 1: Formulation of Fenofibrate Solid Dispersion.

FORMULATION	FENOFIBRATE (mg)	POLYVINYL PYRROLIDONE(mg)	SPAN 80 (ml)	TWEEN 80 (ml)	SODIUM LAURYL SULPHATE(mg)
F1	40	40	0.75	0.75	75
F2	40	40	1.5	0	75
F3	40	40	0.75	1.5	0
F4	40	40	0.75	1.5	150
F5	40	40	0	0.75	0
F6	40	40	1.5	0.75	0
F7	40	40	0.75	0	0
F8	40	40	0.75	0	150
F9	40	40	1.5	1.5	75
F10	40	40	0	0	75
F11	40	40	1.5	0.75	150
F12	40	40	0	0.75	150
F13	40	40	0	1.5	75

2.2.3 Characterization of developed formulations

- **Physical appearance**

The prepared solid dispersion formulations were inspected visually for their colour, homogeneity, consistency and grittiness.

- **Determination of percentage yield**

Percentage yield was calculated for each batches of solid dispersion with respect to theoretical yield and practical yield.

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

- **Estimation of drug content in solid dispersion**

Sample containing 500 mg 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.[6]

- **Determination of Micromeritic properties**

Bulk density

The bulk density is used as a measure to describe packing materials or granules. Bulk density is the ratio of given mass of powder and its bulk volume.

$$Bulk\ density\ \rho_b = \frac{Weight\ of\ powder}{Bulk\ volume}$$

Tapped density

Tapped density is the tapping of the powder in the graduated cylinder until no longer settles. It refers to the bulk density of the powder after a specified comparison process, usually involving vibration of the container.

Determination of angle of repose

It is defined as the maximum angle possible between the surface of the pile ofpowder and the horizontal plane.

Angle of repose (θ) = $\tan^{-1}$(h/r)

Where, θ is the angle of repose
h is the height in cm
r is the radius in cm

Procedure

The powder mixture was allowed to flow through the funnel with its tip fixed to stand at a definite height (h) from a graph paper placed on a horizontal surface. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

Carr's index

The bulk density is the measurement of weight to the volume of the sample. Tapped density is determined as the measurement of weight of the sample to the volume after tapping the measuring cylinder for 500 times from a height of 2 inches. The percentage compressibility (Carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to the tapped density.

$$Carr's\ index = \frac{Tapped\ density - bulk\ density}{Tapped\ density} \text{ x } 100$$

Hausner's ratio

Hausner's ratio : Hausner's ratio is the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better is the flow property.

Procedure

- Accurately weighed 50 g of powder sample into graduated cylinder.
- From this the bulk density and tapped density were calculated. Substitued the values into the equations of Hausner's equation.
- It measures the flow properties of powders.

$$Hausner's\ ratio = \frac{100}{100 - c}$$

***In vitro* dissolution study**

Dissolution test was carried out using USP Type II Dissolution apparatus (paddle type). The stirring rate was 50 rpm. 900 ml of pH 7.4 phosphate buffer was used as a dissolution medium which was maintained at 37±0.5°C. 1 ml samples were withdrawn at 10 minutes interval for 60 minutes which was replaced with 900 ml of pH 7.4 phosphate buffer and was maintained at 37 ± 0.5°C. 1 ml of sample from each tube was withdrawn at the intervals of 0, 10, 20, 30, 40, 50, 60 and replaced with 1 ml of fresh dissolution medium. The collected samples were analysed and absorbance was measured at 286 nm by using UV spectrophotometer.[6][8]

2.2.4 Optimization study

Optimization of the formulations were studied by Box-Behnken design. The amount of span 80 (X1), tween 80 (X2) and sodium lauryl sulphate (X3) were selected as independent variables and the dependent variables were *in vitro* drug release and drug content. The obtained were treated using Design expert version 13.0.7.0 version Software and analysed statistically using analysis of variance (ANOVA).[9][10] The data were also subjected to 3-D response surface methodology to study the effect of span 80, tween 80 and sodium lauryl sulphate on the dependent variables.

Evaluation of Optimized formulation

The batch which was selected from the solutions obtained by optimization study was further evaluated for drug release kinetics and stability study.

2.2.5 Kinetic studies

To examine the drug release kinetics and mechanism, the cumulative % drug release data were fitted to models representing zero order, first order, Higuchi's model and Korsmeyer-Peppas model respectively. The best fit kinetic model was determined from R^2 values.

2.2.6 Stability studies

From the prepared Fenofibrate solid dispersion, best formulation with highest *in vitro* drug release pattern and

drug content was subjected to stability studies. This study was carried out at temperature and humidityconditions as per ICH guidelines and the tests were carried out in a stability chamber. The temperature and humidity conditions used were,

1) 25°C ± 2°C at 75% ± 5% RH
2) 40°C ± 2°C at 75% ± 5% RH

Samples were withdrawn at 30 days intervals for a period of 3 months and evaluated for physical appearance drug content and *in vitro* drug release.

3. RESULTS AND DISCUSSION

Preformulation studies

- **Organoleptic proeperties**

Characterization of API was performed and it was found that all are within the range specified in the pharamacopoeia.

Melting point

Melting point of Fenofibrate was determined by capillary fusion method. It was found to be 80°C ± 1.

- **Caliberation curve of Fenofibrate**

The absorbance of the solutions were measured at 286 nm using UV-visible spectrophotometer. A graph of concentration vs absorbance was plotted. The concentrations and its absorbances were subjected to linear regression analysis and the regression equation was found to be y = 0.0066x-0.0063 and correlation coefficient (R^2) was found to be 0.9948.

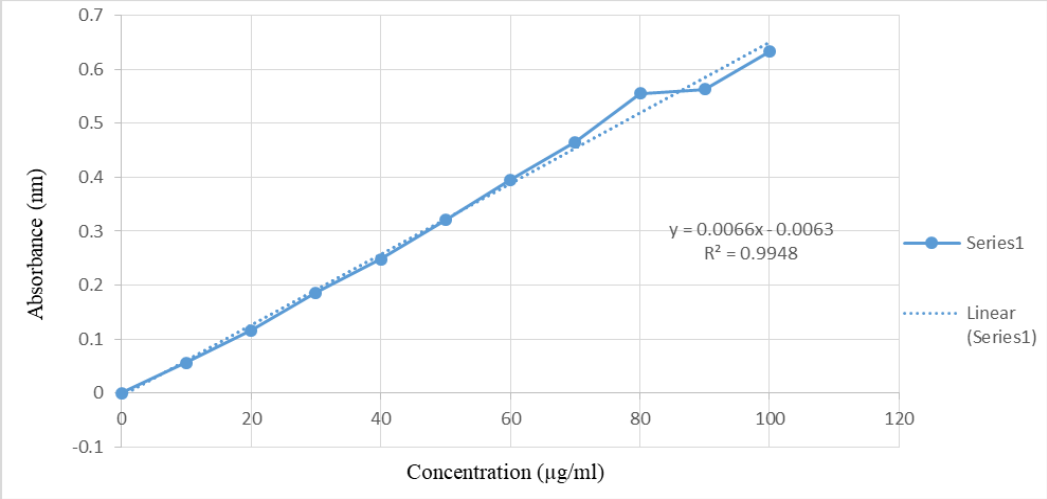

Figure No: 1 Standard Caliberation Curve of Fenofibrate In Ph 7.4 Phosphate Buffer.

- **Solubility study**

It is found that the solubility of Fenofibrate was higher in ethanol, acetone and pH 7.4 phosphate buffer than distilled water and pH 1.2 buffer. So pH 7.4 phosphate buffer was chosen as dissolution media for in vitro dissolution studies.

- **Drug excipient compatibility study (FTIR)**

The FTIR studies were shown in figure numbers 2, 3, 4, 5 & 6. From the results it was revealed that there is no chemical incompatibility between drug and excipients from FTIR studies.

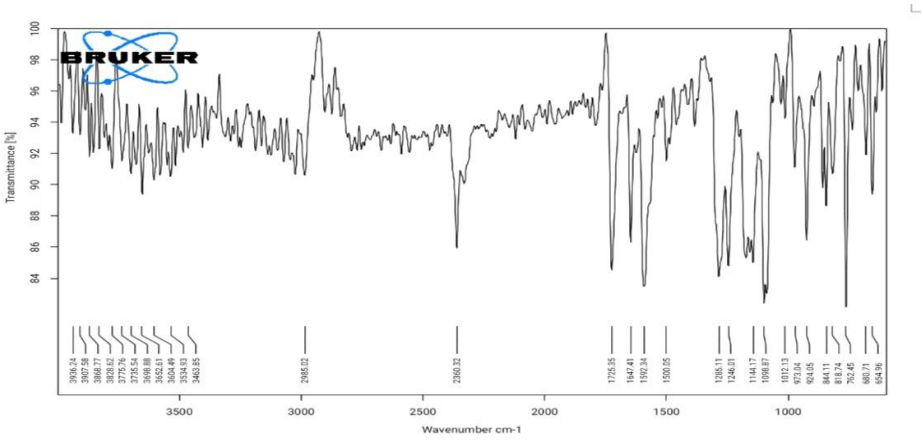

Figure No: 2 Ftir Spectrum Offenofibrate.

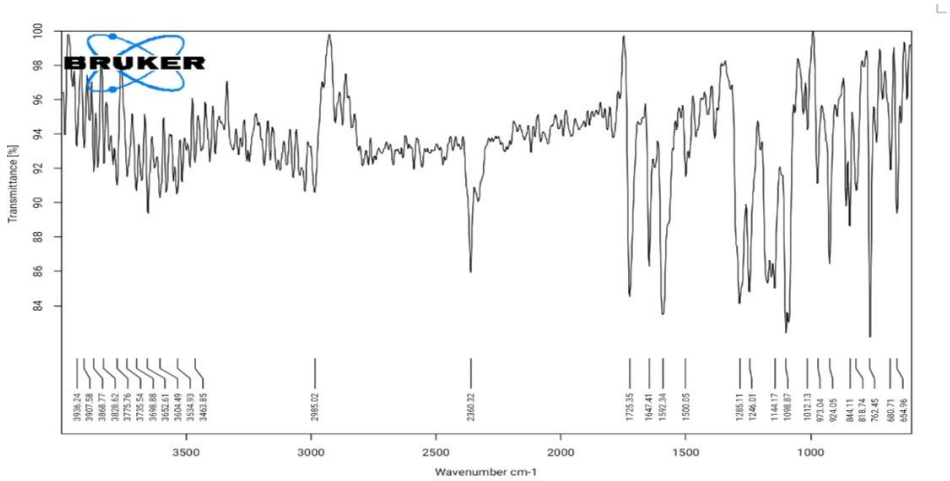

Figure No: 3 Ftir Spectrum of Fenofibrate + PVP K30.

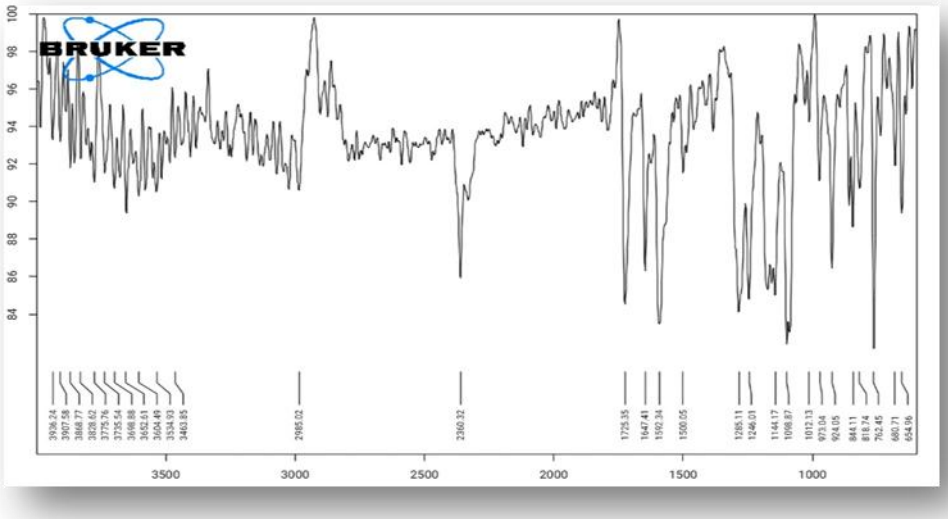

Figure No: 4 Ftir Spectrum of Fenofibrate + SPAN 80.

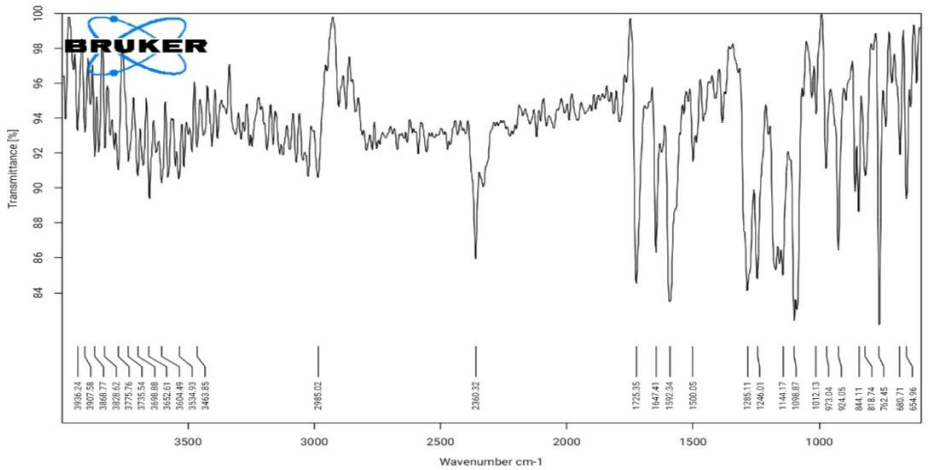

Figure No: 5 Ftir Spectrum of Fenofibrate + TWEEN 80.

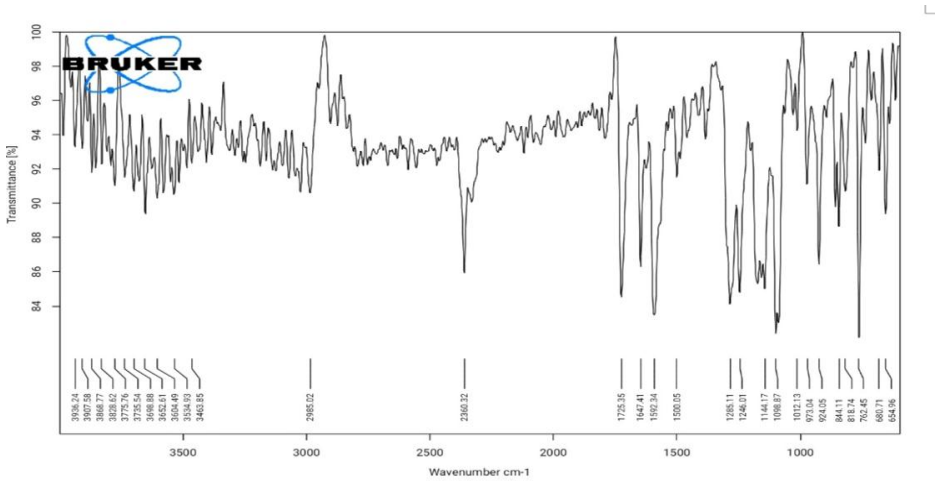

Figure No: 6 Ftir Spectrum of Fenofibrate +SLS.

Characterization of Developed formulations

- **Physical appearance**

Dried white granules, non sticky in nature, excellent flow property.

- **Determination of micromeritic properties**

Table No. 2: Micromeritic Properties of Formulations.

BATCH CODE	ANGLE OF REPOSE ±SD (θ)	BULK DENSITY ±SD (g/ml)	TAPPED DENSITY ±SD (g/ml)	CARR'S INDEX ±SD (%)	AVERAGE HAUSNER'S RATIO
F1	24.51±0.453	0.534±0.003	0.704±0.025	10.099±0.103	1.115±0.001
F2	25.08±0.921	0.548±0.051	0.720±0.003	13.417±0.002	1.201±0.024
F3	26.02±0.131	0.548±0.022	0.723±0.001	13.853±0.002	1.252±0.011
F4	23.63±0.115	0.532±0.005	0.701±0.101	10.051±0.182	1.052±0.001
F5	26.85±0.646	0.557±0.141	0.727±0.031	16.314±0.001	1.322±0.048
F6	26.51±0.241	0.550±0.063	0.724±0.022	14.715±0.015	1.291±0.085
F7	26.22±0.910	0.559±0.001	0.729±0.001	17.613±0.003	1.350±0.002
F8	25.83±0.138	0.545±0.082	0.719±0.083	12.715±0.012	1.147±0.014
F9	24.28±0.914	0.540±0.181	0.708±0.141	11.513±0.157	1.169±0.025
F10	26.10±0.571	0.553±0.015	0.725±0.072	15.613±0.004	1.314±0.018
F11	23.26±0.523	0.539±0.192	0.703±0.004	10.092±0.150	1.079±0.001
F12	25.20±0.249	0.542±0.074	0.711±0.185	12.364±0.002	1.183±0.005
F13	25.43±0.632	0.546±0.001	0.719±0.015	13.010±0.110	1.189±0.041

All values are expressed as mean ± SD, n=3

Micromeritic studies include angle of repose, bulk density, tapped density, carr's index and Hausner's ratio. All the datas given to the table belongs to the range specified in the official monograph. From the datas concluded that Fenofibrate solid dispersion having excellent flow property.

- **Determination of percentage yield**

The percentage yield for various formulations were calculated and shown in table no 3. The results revealed that the percentage yield was high in F4 solid dispersion and the least value found in F7 solid dispersion.

Table No. 3: Percentage Yield of Formulations.

BATCH	PERCENTAGE YIELD (%)
F1	93.58 ± 0.214
F2	88.62 ± 0.163
F3	87.49 ± 0.122
F4	96.31 ± 0.155
F5	83.90 ± 0.182
F6	86.10 ± 0.271
F7	82.57 ± 0.085
F8	89.93 ± 0.174
F9	92.47 ± 0.263
F10	84.28 ± 0.110
F11	94.76 ± 0.158
F12	90.07 ± 0.129
F13	89.16 ± 0.133

All values are expressed as mean ±SD, n=3

Table No. 4: Drug Content of Formulations.

BATCH	DRUG CONTENT (%)
F1	93.65 ± 0.125
F2	91.51 ± 0.224
F3	91.09± 0.153
F4	95.11 ± 0.125
F5	89.50 ± 0.102
F6	90.71 ± 0.193
F7	88.45 ± 0.111
F8	92.06 ± 0.123
F9	92.94 ± 0.105
F10	89.31±0.251
F11	94.85 ± 0.123
F12	92.75 ± 0.152
F13	91.85 ± 0.214

All values are expressed as mean ±SD, n=3.

- **Estimation of drug content in solid dispersion**

The drug content for various formulations were calculated andshown in table no.4. The results revealed that the drug content was high in F4 solid dispersion.

- ***In vitro* dissolution study of solid dispersion**

In vitro dissolution study was carried out with surfactants prepared by solvent evaporation method in various ratios. From the results obtained, the percentage drug released at the end of 60 minutes was found to be high in F4 solid dispersion. ie, 99.5±0.142%.

Table No. 5: *In Vitro* Drug Release Study of Formulations.

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	34.10 ± 0.211	31.86 ± 0.141	31.25 ± 0.185	35.08 ± 0.105	30.08 ± 0.135	30.95 ± 0.145	29.81 ± 0.115	32.99 ± 0.122	33.81 ± 0.211	30.52 ± 0.114	34.36 ± 0.002	33.22 ± 0.115	32.36 ± 0.122
20	36.45 ± 0.158	34.26 ± 0.181	34.05 ± 0.120	37.12 ± 0.113	32.16 ± 0.182	33.71 ± 0.110	31.54 ± 0.251	35.05 ± 0.125	36.08 ± 0.123	33.01 ± 0.255	36.81 ± 0.217	35.46 ± 0.115	34.73 ± 0.281
30	53.83 ± 0.121	50.36 ± 0.135	49.85 ± 0.253	54.40 ± 0.151	47.55 ± 0.154	49.08 ± 0.135	47.35 ± 0.122	51.85 ± 0.146	52.61 ± 0.163	48.18 ± 0.114	53.66 ± 0.125	52.15 ± 0.104	51.16 ± 0.104
40	71.18 ± 0.126	68.58 ± 0.254	67.65 ± 0.141	72.15 ± 0.144	64.05 ± 0.113	66.15 ± 0.262	63.15 ± 0.240	69.61 ± 0.244	70.86 ± 0.125	65.01 ± 0.123	71.62 ± 0.254	70.26 ± 0.124	69.45 ± 0.103
50	91.75 ± 0.135	89.15 ± 0.125	89.33 ± 0.123	92.41 ± 0.272	87.01 ± 0.245	88.71 ± 0.123	86.51 ± 0.201	90.75 ± 0.122	91.35 ± 0.142	88.26 ± 0.125	92.16 ± 0.122	91.39 ± 0.125	90.33 ± 0.114
60	97.41 ± 0.210	94.74 ± 0.204	94.10 ± 0.154	99.55 ± 0.142	92.76 ± 0.202	93.85 ± 0.103	92.21 ± 0.113	95.41 ± 0.112	97.02 ± 0.114	93.25 ± 0.252	98.53 ± 0.113	96.62 ± 0.274	95.16 ± 0.114

All values are expressed as mean ±SD, n=3

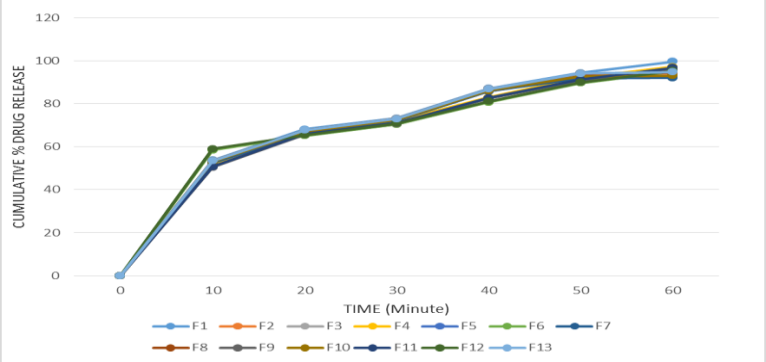

Figure No: 7 *In Vitro* Drug Release of Formulation.

Optimization

The formulation is optimizd by Design expert Software version 13.0.7.0. Box-Behnken design was used to find the optimized formulation. 13 formulations were suggested by the software and after optimization of the analyzed data, 9 solution was obtained. From the solutions, one was selected by considering the *in vitro* dissolution and drug content. The batch with Span 80 0.75 ml, Tween 80 1.5 ml and SLS 150 mg with desirability 0.975 was found to be optimum. From this data, formulation F4 was selected as the optimized formulation. The formulation F4 showed highest value for in vitro dissolution and drug content. Hence, the data obtained from the *in vitro* drug release was fitted to various kinetic models and stability studies were conducted on selected formulation as per ICH guidelines.

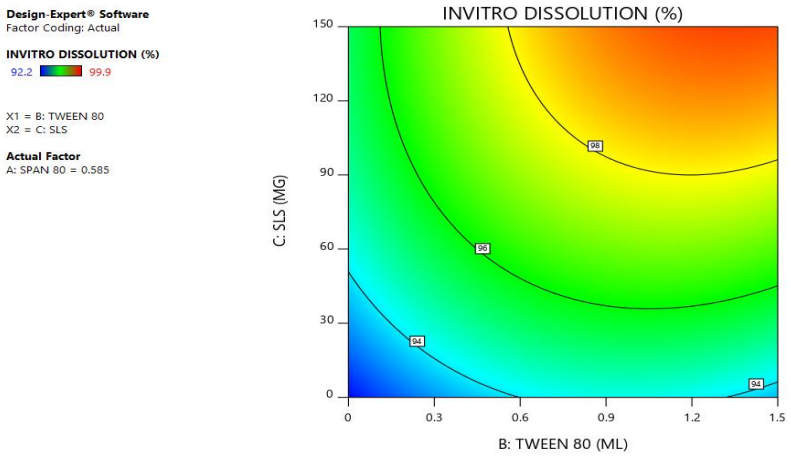

Figure No: 8 Contour Plot Showing The Effect of Tween 80and Sls On *In Vitro* Dissolution.

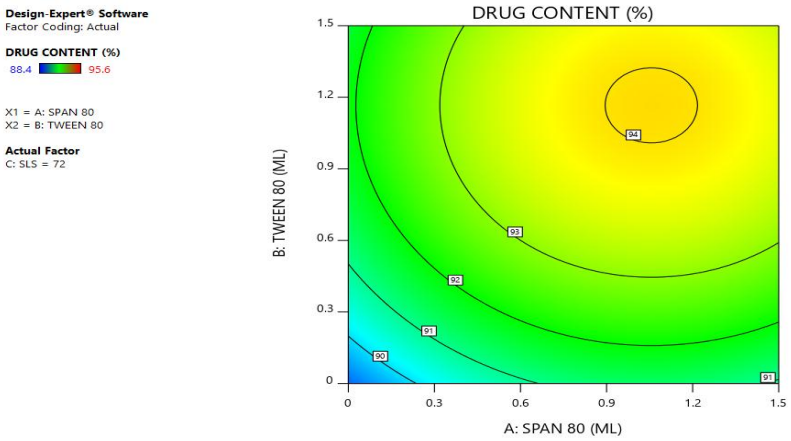

Figure No: 9 Contour Plot Showing The Effect of Span 80 And Tween 80 On Drug Content.

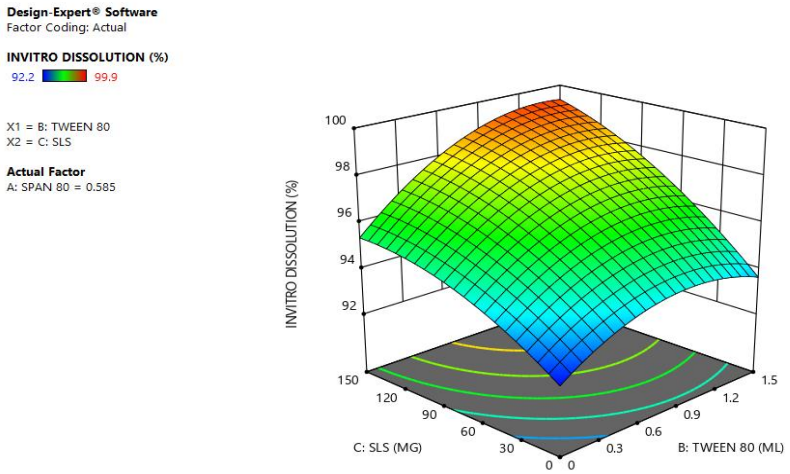

Figure No: 10 3-D Surface Plot Showing The Effect of tween 80 And Sls On In Vitro Dissolution.

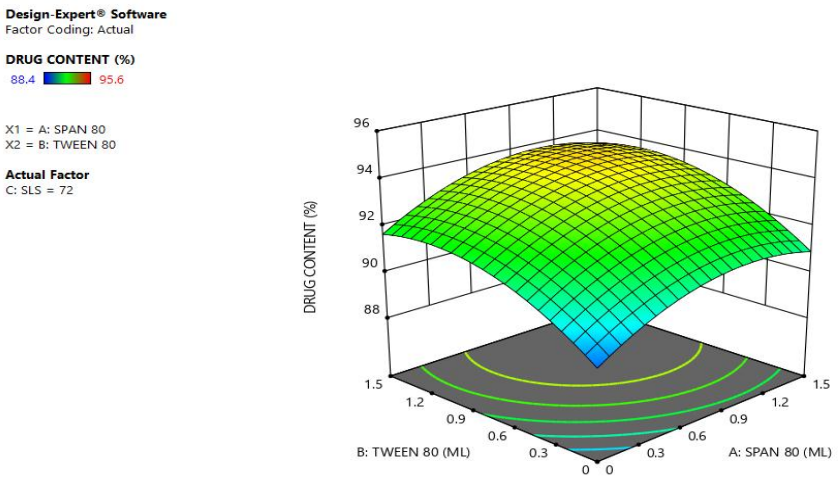

Figure No: 113-D Surface Plot Showing The Effect of Span 80and Tween 80 Ondrug Content.

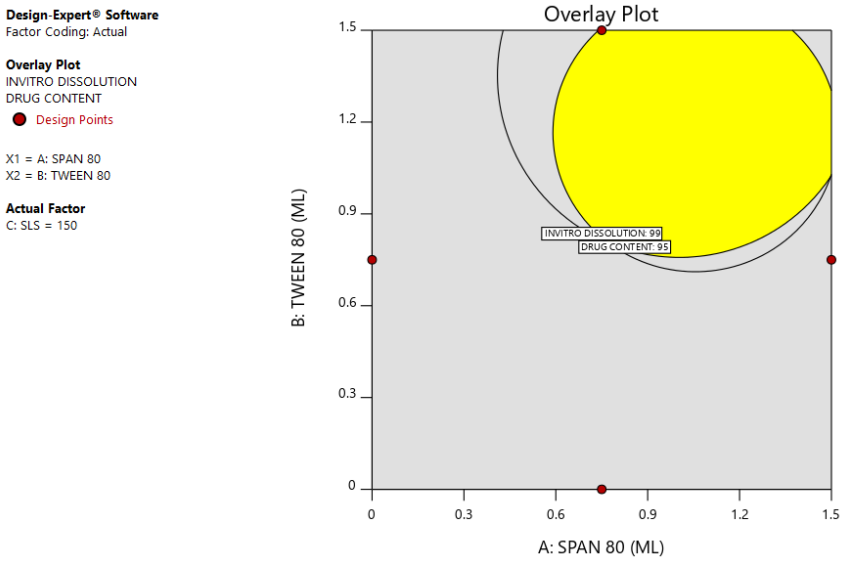

Figure No: 12 Overlay Plot.

Kinetic model for optimized formulation

The dissolution kinetics of optimized formulation was studied. The best fit model with highest R^2 value was the zero order model. To confirm the exact mechanism of drug release from solid dispersion, data was fitted according to Korsmeyer-peppas plot. The n exponent value of best batch was found to be 0.961. Hence it shows no-fickian case II transport mechanism.

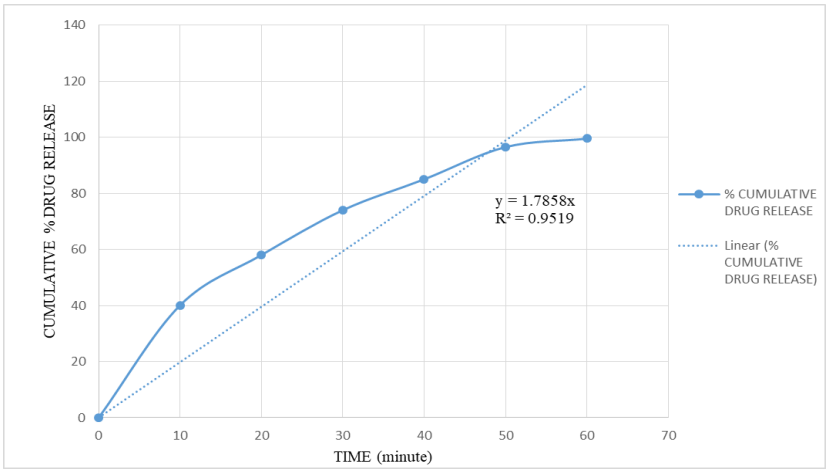

Figure No: 13 Zero Order Release Model.

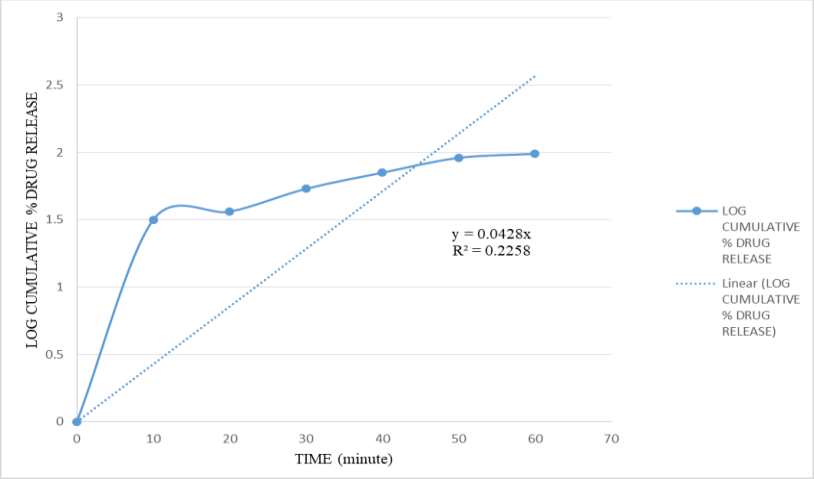

Figure No: 14 First Order Release Model.

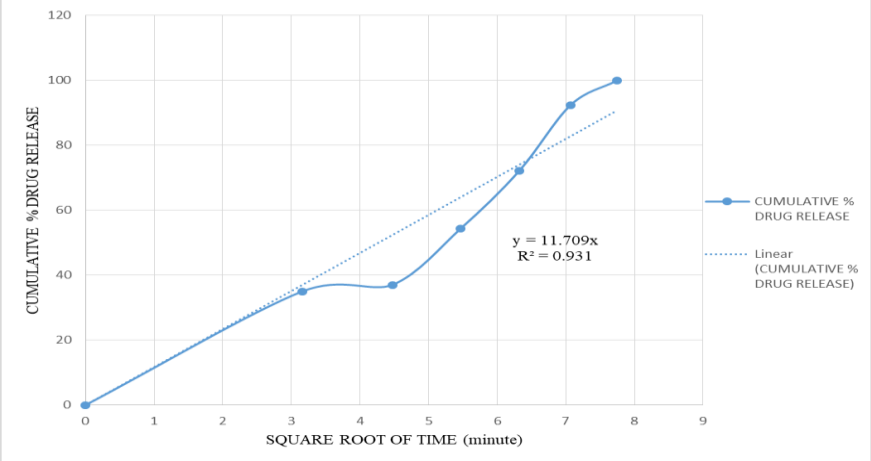

Figure No: 15 Higuchi Release Model.

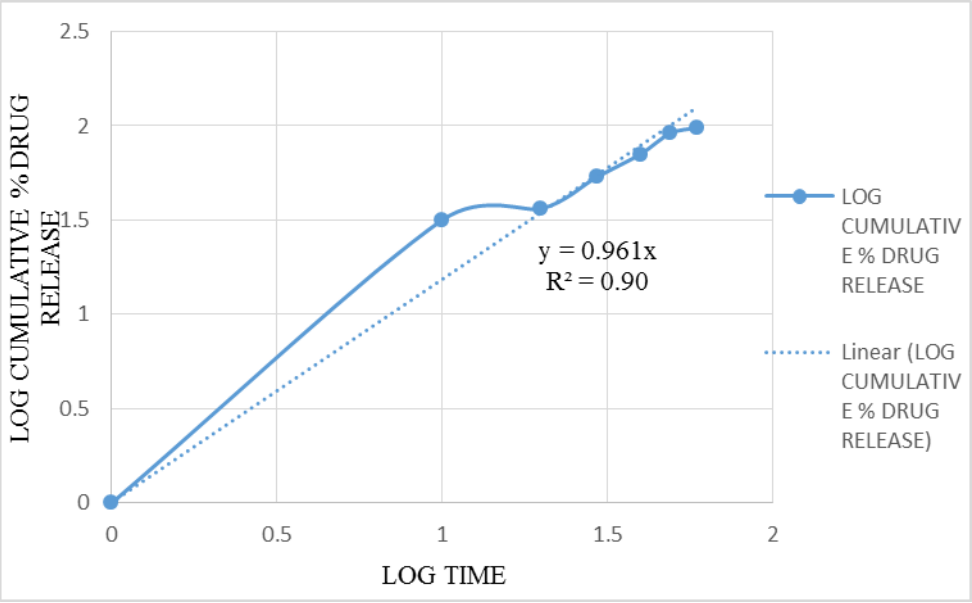

Figure No: 16 Korsmeyer-Peppas Release Model.

Stability studies

The optimized formulation was evaluated after storage at room temperature (25° C ± 2°C/75% ± 5% RH) and elevated temperature (40°C ± 2°C / 75% ±5%RH) in stability chamber. Results have been given in table no:6. From the stability studies after 90 days, it was found that there was no significant change in physical appearance, drug content, and in vitro drug release.

Table No. 6: Stability Data for F7 Formulation.

STORAGE CONDITION	SAMPLING INTERVAL	PHYSICAL APPEARANCE	DRUG CONTENT (%)	IN VITRO DISSOLUTION (%)
25°C ± 2° C 75% ± 5% RH	Initial study	White	95.11±0.125	99.55±0.142
	30 days	White	95.02±0.102	_
	60 days	White	95.00±0.131	_
	90 days	White	94.85 ± 0.232	99.14±0.101
40°C ± 2°C 75% ± 5% RH	Initial study	White	95.11±0.125	99.55±0.142
	30 days	White	95.00 ± 0.103	_
	60 days	White	94.96 ± 0.225	_
	90 days	White	93.72 ± 0.265	97.15 ± 0.140

CONCLUSION

Fenofibrate solid dispersions were successfully developed using span 80, tween 80 and SLS as surfactants with simple and feasible manufacturing process. FT-IR studies for drug and excipients revealed that there is no incompatibility or interaction between drug and excipients. The solid dispersion (F4) prepared using surfactants span 80, tween 80 and SLS in combination was found to show better result and hence selected as optimized formulation. The rate of drug release follows Zero order kinetics and Korsmeyer – Peppas model. F4 was subjected to stability studies under 2 different conditions. From the stability studies after 90 days, it was found that there was no significant change in appearance, drug content and in vitro drug release at normal storage condition. But there was a significant changes observed at accelerated storage condition. The non ionic surfactants span 80 and tween 80 in 1:2 ratio with the combination of anionic surfactant SLS provided better drug release. Thus, the formulation can be a better alternative used to treat hypercholesterolemia in patients suffering from heart diseases and diabetic complications through oral administration. It can be concluded that the study improved solubility, dissolution rate and oral bioavailability. Hence, it is a best formulation for the delivery of a hydrophobic drug like Fenofibrate.

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