Formulation and evaluation mouth dissolving tablets of solid dispersion of fenofibrate

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ABSTRACT

Fenofibrate is a drug of the fibrate class. It is a widely used hypolipidemic drug. The poor aqueous solubility of the drug leads to variable dissolution rates. It is slightly soluble in water. The present investigation was to develop and characterize mouth dissolving tablets of fenofibrate using solid dispersion technique. Mouth dissolving tablets of solid dispersion of Fenofibrate were prepared using different superdisintegrating agents like Cross Carmellose Sodium, Sodium Starch Glycolate and Cross povidone in different concentrations using direct compression method.

The formulation of solid dispersion prepared by solvent evaporation technique by using polymers like PEG 4000 and PEG 6000 respectively in various ratios such as Fenofibrate and PEG 4000 (1:1, 1:2, 1:3, 1:4, 1:5); Fenofibrate and PEG 6000 (1:1, 1:2, 1:3, 1:4, 1:5). Solid dispersion prepared by using PEG 6000 improved solubility & dissolution rate of Fenofibrate as compared to pure drug. Hence F10 formulation of PEG 6000 is selected for further formulation of mouth dissolving tablets. Then, nine batches of mouth dissolving tablets of optimized solid dispersion of fenofibrate are prepared with different concentrations of superdisintegrants of cross carmellose, sodium starch glycolate, cross povidone. The wetting time was observed to be very fast with batch F9 tablets which contain cross povidone. The total drug from the optimized batch was found to be released within the first ten minutes of dissolution study. These tablets rapidly dissolved (within 60-70 sec) in saliva. The prepared tablet gives benefit in terms of patient compliance, low dosing, rapid onset of action, increased bio-availability, low side effect and good stability which make these tablets popular as a dosage form for the treatment of hyperlipidemia.

KEYWORDS

Mouth dissolving tablet, direct compression, Fenofibrate, super disintegrants, cross povidone, wetting time.

INTRODUCTION

The oral route remains the favored route for administration of therapeutic agents thanks to accurate dosage, low cost therapy, self medication, non invasive method and straightforward administration leading to high level of patient compliance. MDTs are known by various names such as "fast-melting, fast-dissolving, oral disintegrating or orodisperse". The European Pharmacopoeia defines the term "orodisperse" as a tablet that can be placed in the mouth where it disperses rapidly before swallowing. Suitable drug candidates for such systems include neuroleptics, cardiovascular agents, analgesics, antiallergics and drugs for erectile dysfunction. In the present study, an attempt was made to develop mouth dissolving tablets of fenofibrate and to investigate the effect of various superdisintegrants on the disintegration time, wetting time and release profile of the drug in the tablets.[4,5]

Mouth dissolving tablets are dosage form, which disintegrate in patient's mouth within a few seconds without the need of water, or chewing, providing best remedy for the patient suffering from dysphasia. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down the stomach. In such cases the bioavailability is greater than those observed for conventional dosage form. The advantages of mouth dissolving dosage form are increasingly being recognized in both industry and academia. The basic approach used in the development of the mouth dissolving tablet is the use of superdisintegrants. Croscarmellose sodium, sodium starch glycolate, and cross povidone were screened in the present study, and the best one was used for further studies.

Fenofibrate (FFA) (isopropyl ester of 2-[4-(4- chlorobenzoyl) phenoxy]-2-methylpropanoic acid) is a widely used hypolipidemic drug available as tablets for oral administration. Each tablet contains 50 mg fenofibrate. The empirical formula is C20H21O4Cl (figure 1) and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79° to 82°C.Fenofibrate is a white solid which is stable under ordinary conditions. Its pharmacological activity consists in reducing triglyceride and cholesterol concentration in plasma. Solubility and permeability are the fundamental parameters controlling the rate and extent of drug absorption. According to the Biopharmaceutics Classification System (BCS), FFA is a Class II having low solubility and high permeability. Bioavailability of FFA solely depends on dissolution rate in the gastrointestinal tract. This drug is used mostly in lipid regulation as it decreases low-density lipoprotein (LDL) and very-low density lipoprotein (VLDL) levels, and increases high density lipoprotein (HDL) level.[7-10]

MATERIALS AND METHODS

MATERIALS

Fenofibrate was supplied as a gift sample from Mylan Laboratories Limited, Sinnar,India.PEG 6000, Cross Carmellose, Sodium Starch Glycolate, Cross Povidone, Mannitol, Saccharin Sodium, Talc, Magnesium Stearate, Vaniline Research lab fine chemical Industry, Mumbai, India. All other chemicals, solvents and reagents were used of either pharmacopoeial or analytical grade.

METHODS

Preformulation Studies of Fenofibrate

Identification and Characterization of Fenofibrate

1. Organoleptic Evaluation

The drug sample as evaluated for its physical properties such as colour, odour, taste, appearance.

2. Melting point

The melting point of drug can be determined by introducing a tiny amount into a small capillary tube, attaching this to the stem of a thermometer centred in a heating bath, heating the bath slowly, and observing the temperature at which drug melted was recorded and compared with the standard.[1-3]

3. Solubility profile

Solubility determination can be done by ultraviolet absorption, nephlometry, Nuclear magnetic resonance and Potentiometric in drug discovery. A drug is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1 to 7.5.[5,7]

4. Loss on drying

Loss on Drying is a back-weighing application used to determine the amount of volatile matter present in tablets, capsules or bulky material. Samples are weighed before and after treatment, and the weight difference is measured. It mainly depends on API and it varies from ingredient to ingredient. But it is preferred to be < 1%. [12,15]

$$\% \text{ LOD} = \frac{\text{Weight of sample before dry} - \text{weight of sample after dry}}{\text{Weight of sample before dry}} \times 100$$

UV Spectroscopic analysis of fenofibrate

Scanning of Fenofibrate in Phosphate Buffer p 6.8 solution

The standard solution (10µg/mL) was scanned from 200-400 nm on UV spectrophotometer (Shimadzu UV–1800). The absorption maxima were found to be at 280 nm. In phosphate buffer Ph 6.8.[13,14]

Preparation of phosphate buffer pH 6.8

The phosphate buffer pH 6.8 was prepared by mixing the 28.20 gm of disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen in sufficient distilled water to produce 1000ml. [9,13]

Procedure

An accurately weighed quantity of fenofibrate was transferred into a 50 mL volumetric flask, diluted up to the mark with phosphate buffer pH 6.8 to get a standard stock solution of 0.5 mg/mL. Aliquot portions of standard stock solution was appropriately diluted to get the concentration of 10µg/mL and scanned in the range 400-200 nm. The zero order spectrum and its first order derivative spectrum were recorded. The calibration curve is shown in figure (10.2) and absorbances of different concentration of fenofibrate are reported in table (10.4)[18-21]

Drug Excipient Compatibility Studies

FTIR Spectroscopy of Fenofibrate, Fenofirate and PEG 6000

FTIR in drug analysis makes an important contribution to the fight against drug-related deaths. Special testing centers, offer drug addicts the possibility to have their drugs checked by FTIR, minimizing the drugs potential damage and preventing overdosing. Identification of Unknown Illegal Substances by FT-IR Spectroscopy. Infrared spectroscopy quickly and reliably identifies legal and illegal substances in-house or on the road. It is ideal for law enforcement, security and safety organizations to save time and money by conducting their own analysis.[22,24]

Formulation and developement

Preparation of solid Dispersion

Solid dispersion of drug and polymer was prepared by using solvent evaporation method with the help of PEG 6000 & PEG 4000 in various ratios.[24]

Solvent Evaporation Method

Table 1. Formulation of drug and polymer

In this method, preparation of solid dispersions fenofibrate with all carriers took place. The ratio of drug and carriers were1: 1, 1: 2, 1: 3, 1:4 and 1:5. The drug and the carriers were dissolved in methanol. The solution was stirred for 1 hour on magnetic stirr. The solvent was evaporated at 40°C in vacuum dryer. After solvent removal, the solid dispersion products were kept in desiccators for 48 hours. The product samples were pulverized using a glass mortar and pestle, sieved through 120 meshes and kept the powder of solid dispersion in desiccators throughout the experimental period. The ratio of drug and carriers were shown in table No.1.[17-20]

Formulation /Batches	Composition	Method	Ratio
F1	Fenofibrate + PEG 4000	Solvent Evaporation method	1:1
F2	Fenofibrate + PEG 4000	Solvent Evaporation method	1:2
F3	Fenofibrate + PEG 4000	Solvent Evaporation method	1:3
F4	Fenofibrate + PEG 4000	Solvent Evaporation method	1:4
F5	Fenofibrate + PEG 4000	Solvent Evaporation method	1:5
F6	Fenofibrate + PEG 6000	Solvent Evaporation method	1:1
F7	Fenofibrate + PEG 6000	Solvent Evaporation method	1:2
F8	Fenofibrate + PEG 6000	Solvent Evaporation method	1:3
F9	Fenofibrate + PEG 6000	Solvent Evaporation method	1:4
F10	Fenofibrate + PEG 6000	Solvent Evaporation method	1:5

Comparative Solubility and Dissolution study to select the optimum batch of solid dispersion

1. Solubility study of solid dispersion and fenofibrate

Solubility measurement of fenofibrate were performed according to published method. The amount of solid dispersion powder containing 2.5 mg equivalents fenofibrate was weighed accurately in volumetric flask was dissolved 5ml distilled water by sonication for 15min, the solutions were filtered through a whatman filter pper no.1. Filtered solution was diluted properly with distilled water. The diluted solution was analysed for fenofibrate in UV at 375 nm. [25]

2. In vitro Dissolution study of Pure Drug and Solid Dispersion

- **Dissolution study of Pure Drug**

The release rate of fenofibrate from fast dissolving tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1 M SLS, at 37 ± 0.50C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus every 2 min. for 30 min, and the samples were replaced with fresh dissolution medium. The samples were filtered through Whatmann filter paper no. 41. Absorbance of these solutions was measured at 290 nm using UV spectrophotometer Shimadzu 1601. To increase the reliability of the observations, the dissolution studies were performed in triplicate.[23,24]

- **Dissolution study of Solid Dispersions prepared by Solvent Evaporation Method**

Dissolution test apparatus type II (Paddle) at rotation speed of 50 rpm was used for the study of dissolution of the drug and solid dispersion was carried out the prepare solid dispersion accurately weight equivalent to the 200mg of drug. The solid dispersion were filled in the empty capsule and analyzed for the drug in the 900 ml dissolution media and 37 ± 0.2 0C. The dissolution media in which performed test ware performed was 0.1 N HCl. solutions. The sample was withdrawn in automatically at time interval 10 min, 20 min, 30 min, 40 min, 50 min, and 60 min. the sample analyzed by UV spectrophotometer at 286 nm. Maximum wavelength of drug against the blank.

- **Comparative Dissolution study of Fenofibrate and solid dispersion**

The dissolution of pure drug is compare with solid dispersions by solvent evaporation method. And graph was plotted to show % drug release which was represented.

Selection of Optimum Batch of Solid Dispersion for formulation of Mouth Dissolving Tablet

For selection of the optimum batch of solid dispersion technique, the dissolution of the pure drug fenofibrate and its solid dispersion by solvent evaporation method with the help of PEG 4000 & PEG 6000 is compare.[16,17]

Evaluation of Solid Dispersion

1. Physical appearance

The prepared solid dispersion was evaluated for visual inspection of all batches of solid dispersion such as colour and appearance.

2. Percentage yield study of solid dispersion

Yield was calculated with respect to dry product. Based on the practical yield (P.Y.) obtained and the calculated theoretical yield (T.Y), % yield was calculated by using the following formula :

P.Y (%) = [Practical weight / Theoretical weight (Drug + Carrier)] ×100

Where,

a = Practical weight of solid dispersion obtained

b = Theoretical weight of solid dispersion prepared

3. Drug Content

Drug content analysis was done by preparing 1 mg/ml solution of the solid dispersions samples in methanol. Samples equivalent to 40 mg of fenofibrate was dissolved in 40ml of methanol. This solution was then kept for 24 h complete extraction of the drug. After 24 hrs, the solution was filtered and a 40 ug/ml solution was prepared with this solution by dilution with methanol. The solution was assayed through UV spectrophotometric method. [19]

$$\% \text{ drug content} = X/Y \times 100$$

X =concentration obtained from spectrophotometer analysis.

Y =Theoretical concentration

4. Different scanning calorimetery studies

DSC thermo gram showed of drug at 82.4°C corresponding to the melting of drug .the physical mixture of endotherm broad and slightly shifted to lower temperature. There was no peak obsevered in the thermo gram of solid dispersions and indicating amorphous form of drug. The DSC of pure fenofibrate, physical mixture and solid dispersion.[10,12]

Formulation of Mouth Dissolving Tablets of Solid Dispersion of Fenofibrate

After evaluation of solid dispersion of fenofibrate preprared by solvent evaluation, mouth dissolving tablets were prepared according to formula given in table 2.

Table 2. Formulation of Mouth Dissolving Tablets

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Solid Dispersion of Fenofibrate (equivalent to 50 mg of drug)	300	300	300	300	300	300	300	300
Cross Carmellose	5	10	15					
Sodium Starch Glycolate				5	10	15		
Cross Povidon							5	10
Magnesium Stearate	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2
Aspartame	2	2	2	2	2	2	2	2
Peppermint	2	2	2	2	2	2	2	2
Mannitol	38	33	28	38	33	28	38	33
Total	350	350	350	350	350	350	350	350

Evaluation of Powder blend for Mouth Dissolving Tablets

Method : Accurate quantity of drug and all ingredients were weighed according to formula and powder except mannitol and magnesium stearate was blended homogeneously in mortar and pestle for 15minutes. Prepared powder blend was passed through sieve No. #60. Finally, mannitol and magnesium stearate passed through sieve No.#30 was added and further mixed for 10 minutes.

The powder blend was evaluated for angle of repose, bulk density, tapped density, compressibility index and hausner's ratio.[9,13]

1.Angle of Repose

Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height, h, was obtained. Diameter of heap, D, was measured. The angle of repose, Ɵ, was calculated by formula

$$\text{Ɵ} = \tan^{-1} (h / r)$$

Where, Ɵ is the angle of repose, h is the height in cm and r is the radius.

2. Bulk Density

Apparent bulk density was determined by pouring presieved drug excipient blend into a graduated cylinder and measuring the volume and weight "as it is". It is expressed in g/ml and is given by

BD = Weight of the powder / Volume of the powder

3. Tapped Density

The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by

TD = Weight of the powder / Tapped of the powder

4. Compressibility Index

It is expressed in percentage and is expressed by

$$\text{Carr's compressibility index (\%)} = [(TD - BD) / TD] \times 100$$

5.Hausner's ratio

It is expressed in percentage and is expressed by

$$H = TD / BD$$

Manufacturing of Mouth Dissolving Tablet of Fenofibrate containing solid dispersion by direct compression method

The SD of Fenofibrate with PEG 6000 simultaneously in 1:4 ratio was prepared by solvent evaporation technique, The drug and the carriers were dissolved in methanol. The solution was stirred for 1 hour on magnetic stirr. The solvent was evaporated at 40°C in vacuum dryer. After solvent removal, the solid dispersion products were kept in desiccators for 48 hours. The product samples were pulverized using a glass mortar and pestle, sieved through 120 meshes and kept the powder of solid dispersion in desiccators throughout the experimental period.[8-11]

The amount of Solid Dispersion complex equivalent to 50mg of drug were taken and then mixed with directly compressible diluents and superdisintegrants in a plastic container. Magnesium stearate and talc were passed through sieve no.60, mixed and blended with the initial mixture in the plastic container followed by compression of the blend. Compression was performed on a tablet compression machine using 8mm punches.[25]

Before tablet preparation, the flow properties and other derived properties evaluated for all the 9 formulations were proved to be within limits showing good flow properties. The physical properties like bulk density, tapped density, angle of repose, compressibility index, and Hausner's ratio were calculated.

Evaluation of Mouth Dissolving Tablets

1. Apperance

The tablets were visually observed for capping, chipping, and lamination.

2. Thickness

Three tablets were selected randomly from each batch and thickness was measured by using Vernier Caliper.

3. Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach). These tablet hardness tests provide a meaningful picture as to the amount of force required to fracture the solid-dose tablet. This knowledge will be useful in gauging the tablet's resistance to damage that might occur during production handling, packaging, and storage.

4.Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated. [5]

$$\textbf{Friability (\%)} = W_1 - W_2 / W_1 \times 100.$$

Where, W_1 = Weight of Tablets (Initial / Before Tumbling)

& W_2 = Weight of Tablets (After Tumbling or friability)

Limit : Friability (%) = Not More Than 1.0 %

5.Drug Content

The Fenofibrate content was estimated as follows :

Method

Twenty tablets were taken randomly and individual tablet were crushed, an amount of the powder equivalent to 50 mg of fenofibrate was dissolved in the 50 ml of 0.1M methanol was added. Shaken for 30 min and added sufficient 0.1 M methanol to produce 100 ml and filtered, diluted suitably and analyzed for drug content at 290 nm using UV-Visible spectrophotometer (UV 1601-Shimadzu, Japan).[4-6]

6.Weight Variation

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight.

7. Disintegration Time

The disintegration time was measured using disintegration test apparatus. One tablet was placed in each tube of the basket. The basket with the bottom surface made of a stainless-steel screen (mesh no. 10) was immersed in water bath at 37 ± 20C. The time required for complete disintegration of the tablet in each tube was determined using a stop watch. To be complied with the pharmacopoeial standards, MDT's must disintegrate within 3 min when examined by the disintegration test for tablets.[2,3]

8. Wetting time

A piece of tissue paper (12cmx10.75cm) folded twice was placed in a Petri dish (Internal Diameter=9cm) containing 6 ml of simulated saliva pH 6.8. A tablet having amaranth powder on the upper surface was placed on the filter paper. Time required to develop red color on the upper surface of tablet was recorded as wetting time. Three tablets from each formulation were randomly selected and the average wetting time was noted. Wetting time corresponds to the time taken for the tablet to disintegrate when placed gently on the tissue paper in a petridish. This method will duplicate the in-vivo disintegration as the tablet is motionless on the tongue. Less is the wetting time indicates more porous the tablets.[3]

9. In-vitro Dissolution studies

The release rate of fenofibrate from mouth dissolving tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml phosphate buffer pH 6.8 , at 37 ± 0.5ºC and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus every 2 min. for 30 min, and the samples were replaced with fresh dissolution medium. The samples were filtered through Whatmann filter paper no. 41. Absorbance of these solutions was measured at 290 nm using UV spectrophotometer Shimadzu 1601. To increase the reliability of the observations, the dissolution studies were performed in triplicate.[5]

10. Stability studies

A series of tests designed to obtain information on the stability of a pharmaceutical product in order to define its shelf-life and utilization period under specified packaging and storage

conditions.Various stability studies like accelerated stability study, intermediate and long term stability studies were done during preformulation. The sample was subjected to higher temperature or humidity or both, to know their impact on the stability of mouth dissolving tablet. The tests that monitor the quality, purity, potency, and identity which could be expected to change upon storage are chosen as stability tests. Therefore appearance, assay, degradation products, microbiological testing, dissolution, and moisture are standard tests performed on stability test samples. The fast dissolving tablets stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.[1-3]

i.40 ± 1°C

ii.50 ± 1°C

iii.37 ±1°C and RH 75% ± 5% T

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization such as visual defects, Hardness, Friability, Disintegrations, and Dissolution etc. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25°C.

The international Conference on Harmonization (ICH) Guidelines titled " Stability testing of new drug substance and products " (QIA) describes the stability test requirements for drug registration application in the Europeans Union, Japan and United States of America. ICH specifies the length of study and storage conditions.

Long-term testing 25ºC ± 2ºC/60 % RH ± 5% For 12 Months.

Short-term testing 30ºC ± 2ºC/65 % RH ± 5% For 1 Months.

Accelerated testing 40ºC ± 2ºC/65 % RH ± 5% For 6 Months.

Stability studies for the present work carried out at 40ºC ± 2ºC/ 75 % ± 5 % RH for the selected formulation for 3 months.

RESULT AND DISCUSSION

1. Preformulation Studies of Fenofibrate

Identification and characterization of Fenofibrate

- **Organoleptic Properties**

Organoleptic evaluation reveals that the sample of Fenofibrate obtained was complied with standards. The result is presented in the table 3.

Table 3. Identification tests of fenofibrate with the reported standards.

Sr.No.	Identification Test	Observation	Inference
1.	Apperance	Fine powder	Complies with IP
2.	Colour	White	Complies with IP
3.	Odour	Odourless	Complies with IP

- **Melting Point**

The Melting point of received drug sample of Fenofibrate was determined and it was found to be 80ºC which is in the range 79º-82ºC so, complies with standard, indicating purity of drug.

- **Solubility Study of Drug**

The descriptive form of solubility profile according to parts of solvent required for 1 parts of solute given in the table 4.

Table 4. Solubility study of Fenofibrate in the different solvents

Sr.No.	Solvent	Solubility (mg/ml)	Inference
1.	Distilled water	0.003	Practically Insoluble
2.	Chloroform	3.20	Sparingly Insoluble
3.	Methylene chloride	29.74	Freely Soluble
4.	Methanol	90.38	Freely Soluble

2. UV Spectroscopic Analysis of Fenofibrate

Scanning of Fenofibrate -The standard solution of Fenofibrate was scanned in the range of 200-400nm in Phosphate buffer 6.8 and absorbance maxima was found at 280nm.

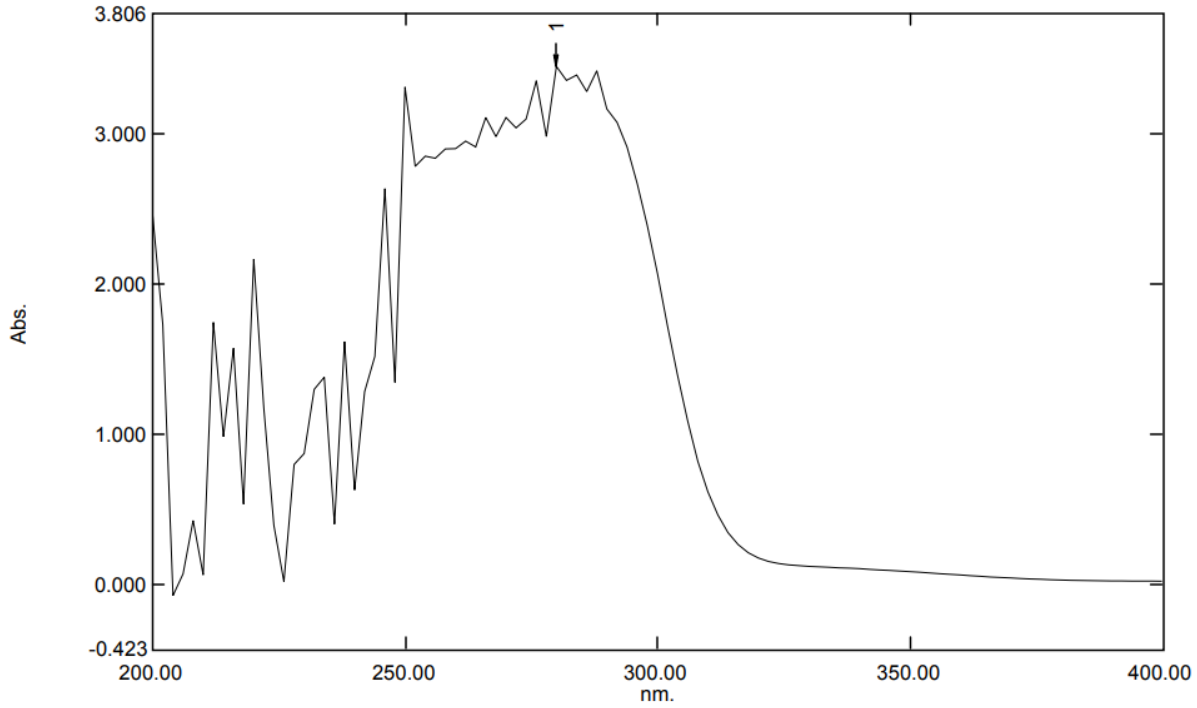


Figure 1. Scanning of Fenofibrate

Table 5. Data for Calibration Curve of Fenofibrate

Sr.No.	Concentration	Absorbance
1	10	0.037
2	20	0.056
3	30	0.083
4	40	0.11
5	50	0.147

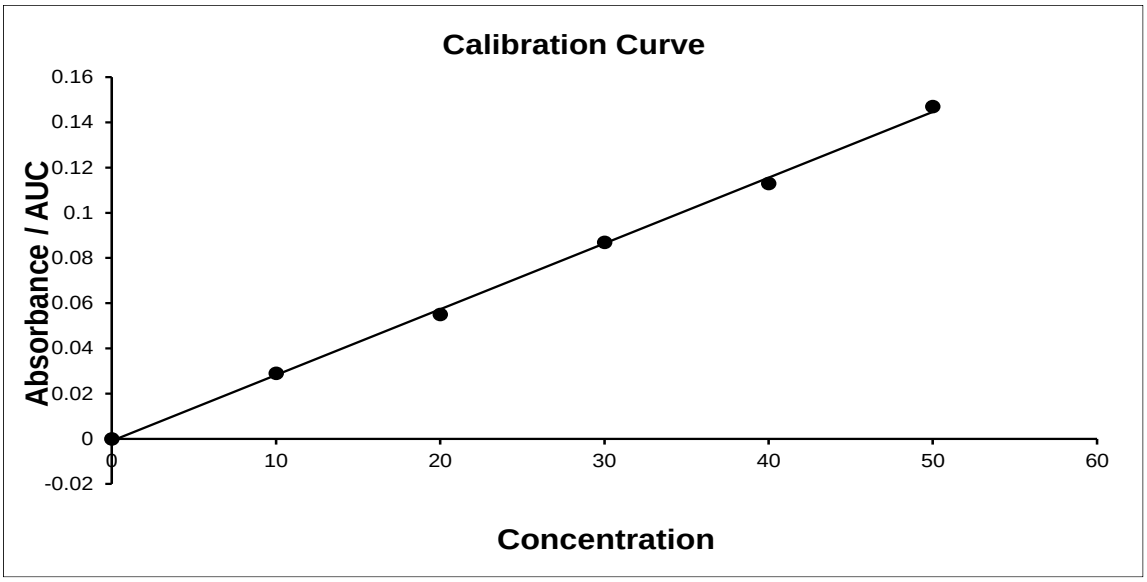
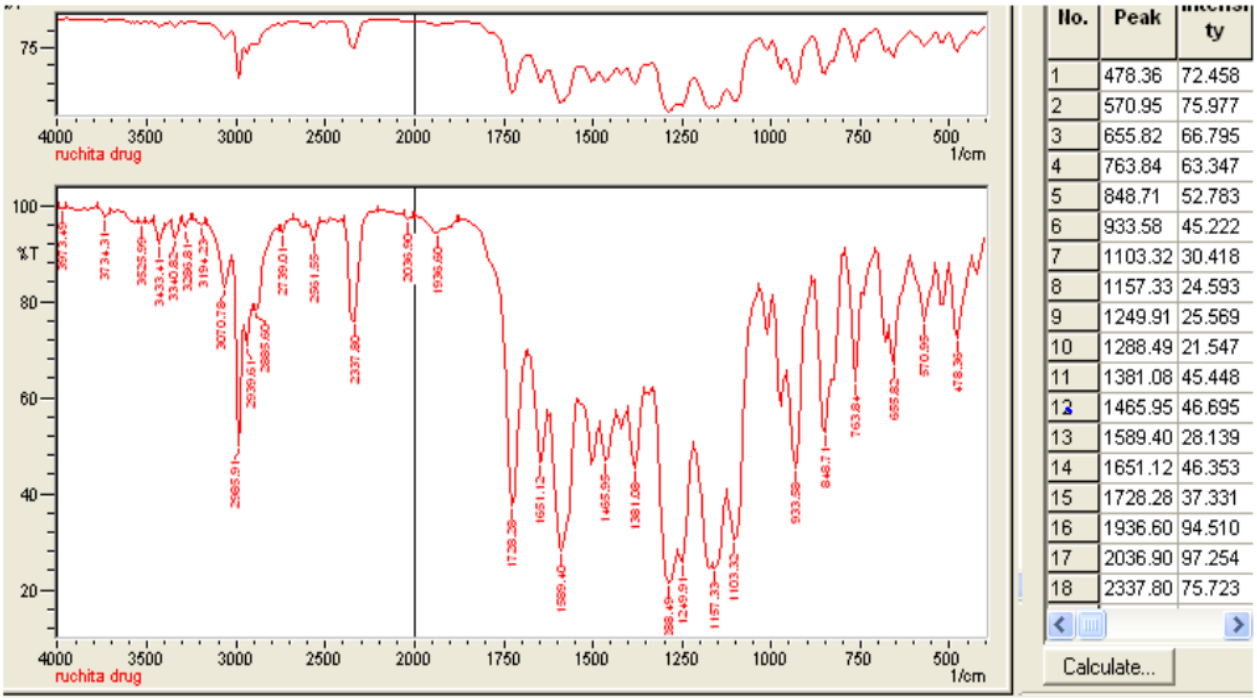


Figure 2. Calibration Curve of Fenofibrate

3. Drug Excipient Compatibility Studies

The FTIR spectrum of pure drug and drug- excipients physical mixture and its interpretation is shown below:

I. FTIR OF Fenofibrate



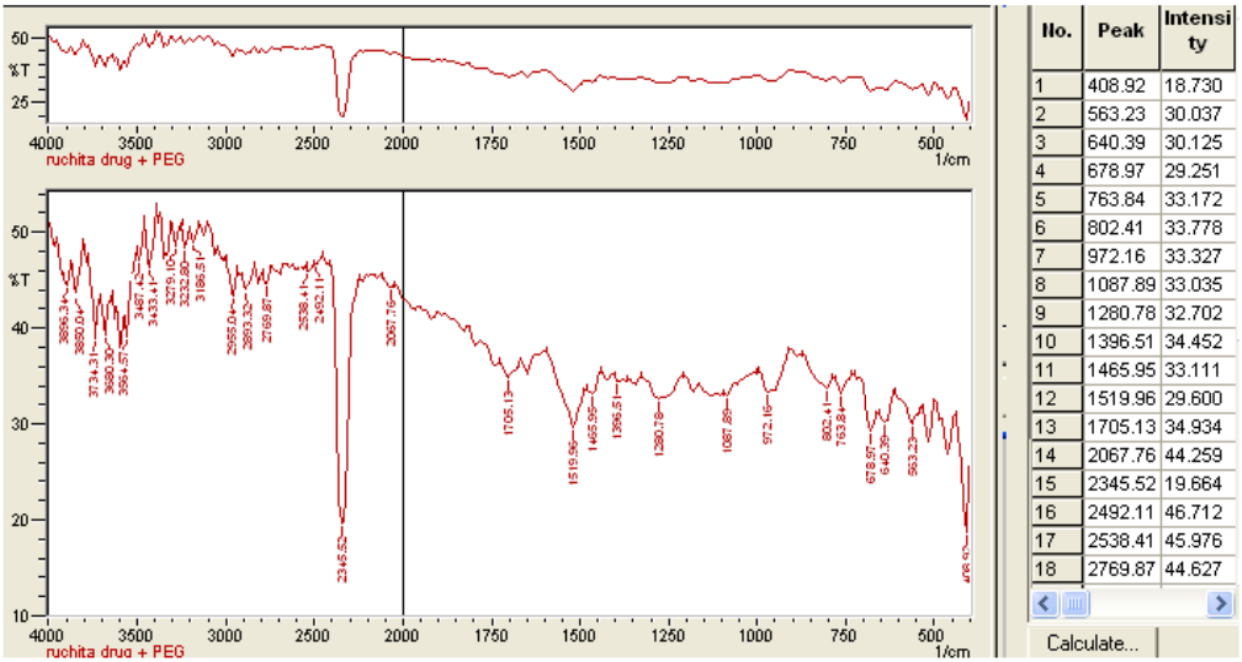
No.	Peak	Intensity
1	478.36	72.458
2	570.95	75.977
3	655.82	66.795
4	763.84	63.347
5	848.71	52.783
6	933.58	45.222
7	1103.32	30.418
8	1157.33	24.593
9	1249.91	25.569
10	1288.49	21.547
11	1381.08	45.448
12	1465.95	46.695
13	1589.40	28.139
14	1651.12	46.353
15	1728.28	37.331
16	1936.60	94.510
17	2036.90	97.254
18	2337.80	75.723

Figure 3. FTIR Spectra of Fenofibrate

Table 6. FTIR Peaks of Fenofibrate

Reference Peak Wavenumber (cm-1)	Observed Peak Wavenumber (cm-1)	Functional Group
1705-1740	1728.28	C=O Stretch
2000-2170	2036.90	C=C Stretch
2300-2500	2337.80	C-H Stretch
3130-3450	3433.41	O-H Stretch

II. FTIR of Fenofibrate + PEG 6000



No.	Peak	Intensity
1	408.92	18.730
2	563.23	30.037
3	640.39	30.125
4	678.97	29.251
5	763.84	33.172
6	802.41	33.778
7	972.16	33.327
8	1087.89	33.035
9	1280.78	32.702
10	1396.51	34.452
11	1465.95	33.111
12	1519.96	29.600
13	1705.13	34.934
14	2067.76	44.259
15	2345.52	19.664
16	2492.11	46.712
17	2538.41	45.976
18	2769.87	44.627

Figure 4. FTIR Spectra of Fenofibrate + PEG 6000

Table 7. FTIR Peaks of Fenofibrate + PEG 6000

Reference Peak Wavenumber (cm-1)	Observed Peak Wavenumber (cm-1)	Functional Group
1705-1740	1705.13	C=O Stretch
2000-2170	2067.76	C=C Stretch
2300-2500	2492.11	C-H Stretch
3130-3450	3433.41	O-H Stretch

FORMULATION AND DEVELOPMENT

PREPARATION OF FENOFIBRATE SOLID DISPERSION

The formulation of solid dispersion prepared by solvent evaporation technique by using polymers like PEG 4000 and PEG 6000 respectively in various ratios such as Fenofibrate and PEG 4000 (1:1, 1:2, 1:3, 1:4, 1:5) ; Fenofibrate and PEG 6000 (1:1, 1:2, 1:3, 1:4, 1:5). Solid dispersions

prepared by using PEG 4000 were F1, F2, F3, F4, F5 and Solid dispersions prepared by using PEG 6000 were F6, F7, F8, F9 and F10 respectively. [7-9]

Comparative Solubility and Dissolution study to select the optimum Batch of Solid Dispersion

Table 8. Solubility study of Fenofibrate and Solid Dispersion

Formulations	Drug : Carrier	Solubility (µg/ml)
Pure Drug	Pure Drug	2.385
F1	Fenofibrate + PEG 4000 (1:1)	60.80
F2	Fenofibrate + PEG 4000 (1:2)	65.96
F3	Fenofibrate + PEG 4000 (1:3)	72.50
F4	Fenofibrate + PEG 4000 (1:4)	80.76
F5	Fenofibrate + PEG 4000 (1:5)	89.54
F6	Fenofibrate + PEG 6000 (1:1)	68.55
F7	Fenofibrate + PEG 6000 (1:2)	70.97
F8	Fenofibrate + PEG 6000 (1:3)	80.56
F9	Fenofibrate + PEG 6000 (1:4)	92.43
F10	Fenofibrate + PEG 6000 (1:5)	95.34

Solubility study of various solid dispersion trial batches was performed. Solid dispersion prepared by using PEG 6000 improved solubilty of Fenofibrate as compared to pure drug. The batch F10 was more soluble than pure drug and other formulation batches.

In vitro Dissolution study of pure drug and Solid Dispersion

Dissolution study of pure drug and solid dispersion batches in phosphate buffer 6.8 was carried out and absorbance was taken in UV spectrophotometer at 280nm. is reported in table no.9.

Table 9. Dissolution profile of drug and solid dispersion

Time (min.) ⇒	**0**	**2**	**4**	**6**	**8**	**10**
Pure Drug	0	5.04±1.22	8.94±0.54	12.15±1.34	17.56±1.56	20.16±0.64

F1	0	20.19±1.13	31.05±1.37	39.98±1.93	50.46±1.94	78.87±0.26
F2	0	19.98±0.98	41.48±0.73	57.93±1.04	68.92±0.84	70.21±0.93
F3	0	32.67±0.65	50.36±1.93	61.95±0.74	71.54±1.45	75.43±0.16
F4	0	33.75±1.74	52.67±0.03	62.74±0.72	70.54±1.84	76.00±1.53
F5	0	35.76±1.84	51.95±0.86	64.50±0.46	69.87±0.56	77.90±1.73
F6	0	26.45±0.03	39.09±0.53	55.87±0.3	67.98±0.53	72.88±0.63
F7	0	31.39±0.83	50.23±1.93	65.47±1.84	71.24±0.24	75.98±0.73
F8	0	36.76±0.76	52.87±1.03	67.88±0.17	72.45±1.87	89.43±1.73
F9	0	39.73±1.20	55.93±0.97	69.93±0.37	78.73±1.95	93.96±1.84
F10	0	39.75±1.03	60.23±0.72	69.38±1.74	84.83±0.756	96.33±0.63

*Results are mean of 3 determinations

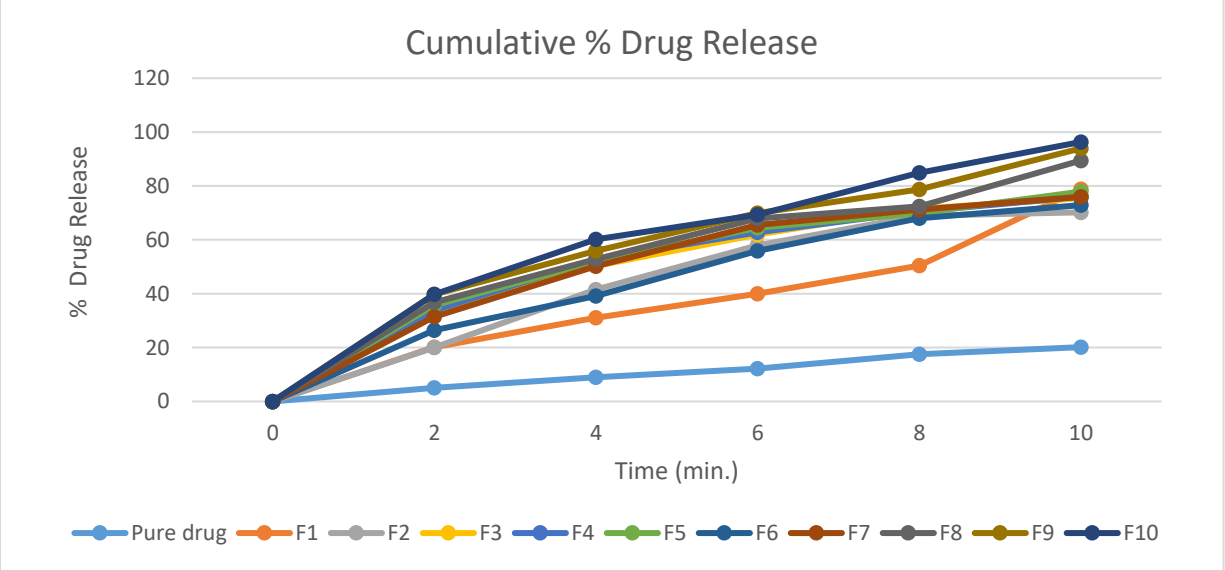


Figure 5. Dissolution profile of pure drug and solid dispersion

Selection of Optimum Batch of Solid Dispersion for formulation of Mouth Dissolving Tablets

From solubility and dissolution studies of all batches of solid dispersion by using PEG 6000 shows improved drug solubility and dissolution rate than PEG 4000, Hence F10 formulation of PEG 6000 is selected for further formulation of mouth dissolving tablets.

Evaluation of Selected batch (F10) of Solid Dispersion

1.Physical Appearance

All batches of solid dispersion were evaluated for color and appearance. The physical appearance of each formulation is shown in table 10.

Table 10. Physical Appearance of formulations Drug and Polymer

Sr.NO.	Formulation	Color	Appearance
1	**F1**	Off White	Powder
2	**F2**	Off White	Powder
3	**F3**	Off White	Powder
4	**F4**	Off White	Powder
5	**F5**	Off White	Powder
6	**F6**	Off White	Powder
7	**F7**	Off White	Powder
8	**F8**	Off White	Powder
9	**F9**	Off White	Powder
10	**F`0**	Off White	Powder

2. Percentage Practical Yield of Solid Dispersion

Table 11. Practical Yield of Solid Dispersion

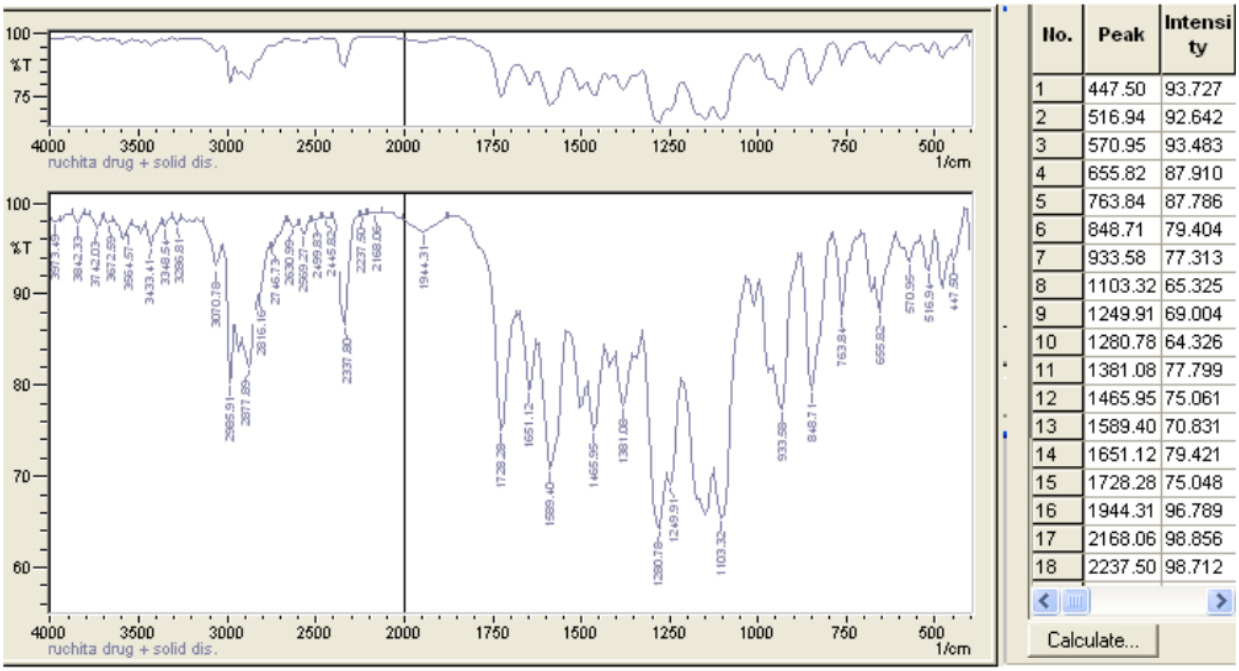
Formulation	Initial weight (mg)	Final weight (mg)	% Practical Yield
F1	2000	1.899	94.96
F2	2750	26367	95.88
F3	3000	2883	96.11
F4	3750	3517	93.80
F5	5000	4722	94.44
F6	4000	3873	96.83
F7	3750	3646	97.23
F8	4750	4689	97.89
F9	5000	4868	97.36
F10	5750	5529	98.16

3. Drug Content of Solid Dispersion of Optimized Formulation F10

The Drug Content of Optimized formulation of Solid Dispersion of Fenofibrate was found to be 99.25% indicating good content in solid dispersion.

4. Characterization of Solid Dispersion

FTIR studies of solid dispersion



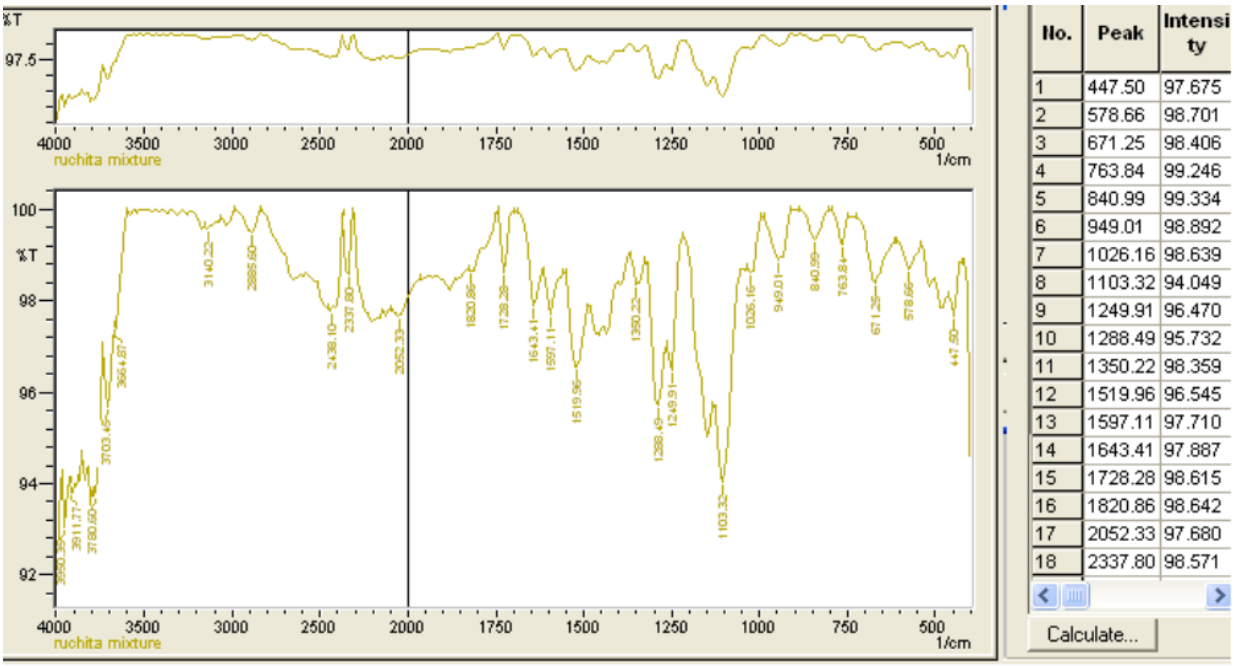
No.	Peak	Intensity
1	447.50	93.727
2	516.94	92.642
3	570.95	93.483
4	655.82	87.910
5	763.84	87.786
6	848.71	79.404
7	933.58	77.313
8	1103.32	65.325
9	1249.91	69.004
10	1280.78	64.326
11	1381.08	77.799
12	1465.95	75.061
13	1589.40	70.831
14	1651.12	79.421
15	1728.28	75.048
16	1944.31	96.789
17	2168.06	98.856
18	2237.50	98.712

Figure 6. FTIR Spectra of Solid Dispersion

Table 12. FTIR Peaks of Solid Dispersion

Reference Peak Wavenumber (cm-1)	Observed Peak Wavenumber (cm-1)	Functional Group
1705-1740	1728.28	C=O Stretch
2000-2170	2168.06	C=C Stretch
2300-2500	2445.11	C-H Stretch
3130-3450	3433.41	O-H Stretch

FTIR studies of Mixture



No.	Peak	Intensity
1	447.50	97.675
2	578.66	98.701
3	671.25	98.406
4	763.84	99.246
5	840.99	99.334
6	949.01	98.892
7	1026.16	98.639
8	1103.32	94.049
9	1249.91	96.470
10	1288.49	95.732
11	1350.22	98.359
12	1519.96	96.545
13	1597.11	97.710
14	1643.41	97.887
15	1728.28	98.615
16	1820.86	98.642
17	2052.33	97.680
18	2337.80	98.571

Figure 7. FTIR Spectra of Mixture

Table 13. FTIR Peaks of Mixture

Reference Peak Wavenumber (cm-1)	Observed Peak Wavenumber (cm-1)	Functional Group
1705-1740	1728.28	C=O Stretch
2000-2170	2052.33	C=C Stretch
2300-2500	2052.33	C-H Stretch
3130-3450	3140.22	O-H Stretch

XRD Studies of Pure Drug and Solid Dispersion

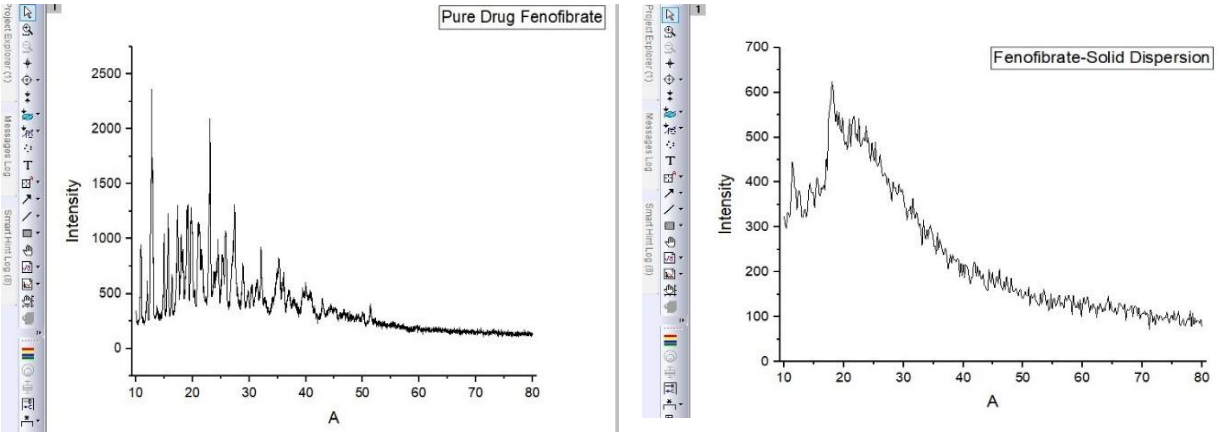


Figure 8. XRD studies

Evaluation of Precompression Properties

For each designed formulation, blend of drug and excipients was prepared and evaluated for precompression properties shown in table 10. Bulk density was found to be between 0.44±0.04 to 0.49±0.01gm/cm3 and tapped density between 0.51±0.01 to 0.570±0.03 gm/cm3 for all formulations. From density data % compressibility was calculated and was found to be between 12.80±0.03% to 16.69±0.04 percent. Angle of repose was found to be in the range of 25.82±0.03 to 32.22±0.02. Hausner ratio was found below 1.22±0.02. All the formulation shows the fair to good flow properties for direct compression and hence tablets were prepared by using direct compression technology.

Table 14. Precompression Properties

Formulation	Angle of repose(o)*	Bulk density (gm/cm3)*	Tapped density (gm/cm3)*	Carr's index (%)*	Hausner's ratio (HR)*
F1	28.41±0.01	0.45±0.03	0.5161±0.02	12.80±0.01	1.146±0.02
F 2	29.34±0.02	0.470±0.02	0.5517±0.01	14.71±0.01	0.8528±0.02
F3	32±0.01	0.444±0.02	0.5330±0.01	16.69±0.02	1.200±0.03
F4	32.47±0.03	0.4637±0.03	05423±0.03	14.49±0.03	0.855±0.01

F5	27.75±0.02	0.4637±0.01	0.5423±0.03	14.44±0.03	1.161±0.03
F6	30.9±0.02	0.4848±0.02	0.5517±0.03	12.12±0.03	1.1379±0.03
F7	30.52±0.01	0.45±0.02	0.5161±0.02	12.80±0.02	1.146±0.01
F8	25.82±0.03	0.477±0.01	0.5517±0.01	13.5±0.03	1.156±0.01
F9	32.22±0.01	0.444±0.03	0.5333±0.01	16.69±0.02	1.200±0.02

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

Evaluation of Post Compression Properties of tablets

Tablets were prepared using direct compression technique. Since the powder material was free flowing, Tablets were obtained of uniform weight due to uniform die fill, tablets were obtained of uniform weight variations as per Pharmacopoeial specifications. All the tablets were exhibit in white color, odorless, convex in shape with smooth surface with zero defects. The drug content was found in the range of 97.56 – 101.32% (acceptable limit) and the hardness of the tablets between 3.5 – 4.2 kg/cm2 . Friability of the tablets was found below 1 % indicating a good mechanical resistance of tablets. Thickness of the formulations were varied from 1.9±0.02 to 2.3±0.02 mm, diameter of the formulations were varied from 9.7±0.01 to 10.1±0.01 mm. All the parameters were found well within the specified limit.

Table 15. Post Compression Paramters

Form-ulation	**Diameter (mm)**	**Thickness (mm)**	**Hardness (kg/cm2)**	**Friability (%)**	**Drug content (%)**	**Weigh variati (mg)**
F1	9.7± 0.12	2.1±0.3	3.5± 0.10	0.30± 0.05	96.35±1.3	403± 0.31
F2	9.84± 0.22	2.2±0.1	4.0± 0.31	0.45± 0.05	97.61±2.34	398± 1.6
F3	9.99± 0.43	2.1±0.42	3.9± 0.42	0.56± 0.12	97.53±1.13	397± 2.04
F4	10.1±	2.4±0.03	3.8±	0.61±	96.22±1.12	404±

	0.52		0.52	0.11		2.23
F5	9.75± 0.31	2.0±0.71	4.1± 0.21	0.55± 0.53	97.75±2.1	397± 2.21
F6	9.83± 032	2.0±0.53	4.2± 0.53	0.45± 0.05	98.75±1.23	400± 0.65
F7	9.97± 0.33	2.4±0.12	3.9± 0.31	0.45± 0.14	98.50±1.2	402± 1.63
F8	9.79± 0.34	2.3±0.42	4.0± 0.63	0.69± 0.03	99.41±1.12	402± 0.82
F9	9.87± 0.12	2.0±0.31	3.9± 0.14	0.61± 0.05	99.51±2.32	405± 0.31

In vitro % Drug Release of Drug from Tablet

All the nine formulations were subjected for the in vitro dissolution studies using tablet dissolution apparatus (USP). Phosphate Buffer pH 6.8 was used as dissolution medium. The sample were withdrawn at different time intervals, filter and analyzed at 280nm. Cumulative % drug release was calculated on the basis of mean amount of Fenofibrate present in respective table.

Table 16. Dissolution Profile of Tablets

Time (min.)	**0**	**2**	**4**	**6**	**8**	**10**
F1	0	34.606±0.13	43.906±01.39	61.244±0.62	84.138±1.37	93.513±0.62
F2	0	32.136±0.07	43.904±1.83	61.244±1.73	84.775±1.94	92.896±1.63
F3	0	33.371±0.12	44.436±0.92	57.941±1.94	75.723±0.78	95.924±1.82
F4	0	29.667±0.73	42.666±0.62	60.002±1.7	83.532±0.53	90.147±1.85
F5	0	28.432±1.73	39.571±0.71	55.675±0.82	78.878±1.98	89.78±0.64
F6	0	30.284±1.73	43.284±1.85	58.157±0.7	76.74±0.82	92.879±0.55
F7	0	31.519±1.94	43.903±1.83	62.476±0.64	85.391±0.62	97.217±0.73
F8	0	32.754±1.92	44.522±1.64	64.333±0.98	86.63±1.73	97.458±1.23
F9	0	33.371±0.92	45.758±0.73	65.567±1.63	87.868±1.53	99.08±0.79

*Results are mean of 3 determinations

The rapid dissolution was observed in formulation F9 releases 99.08±0.79 at the end of 10minutes. Rapid dissolution might be due to fast breakdown of particles and rapid absorption of drug.

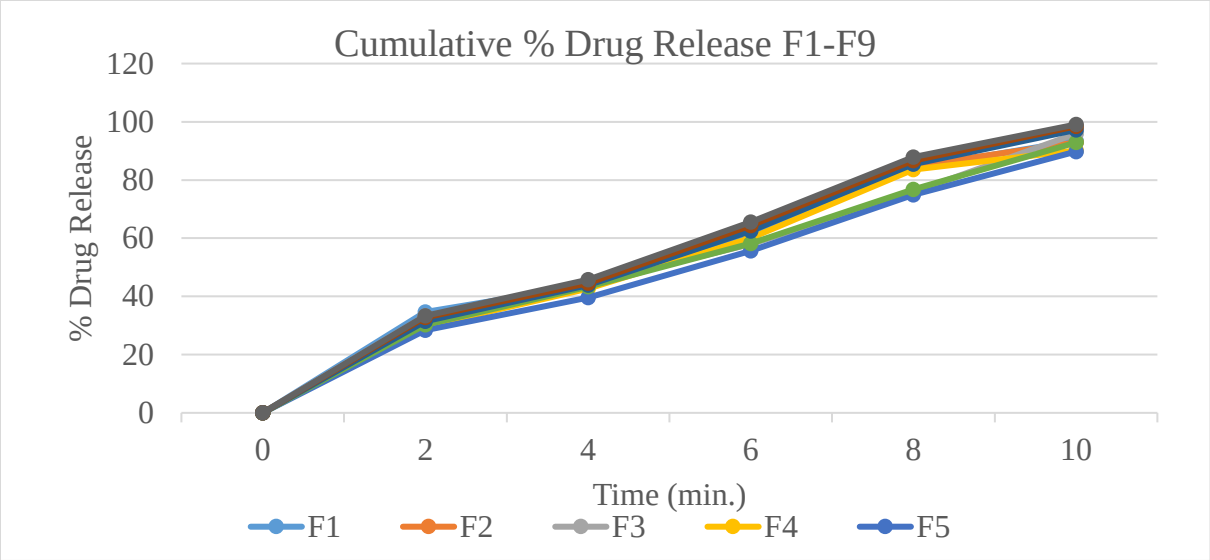


Figure 9. Dissolution Profile of Tablets

In comparative study F9 formulation gives higher percentage drug release compare to other remaining eight formulations at the end of 10minutes and graphical representation is shown in figure 9. Therefore it was concluded that the best batch was found to be F9 because of lesser disintegration time and highest % drug release at the end of 10 min.among all the formulations. Because it contain Crosspovidon superdisintegrant with fast wetting time and highest swelling property.

Stability Study

The mouth dissolving tablets of solid dispersion of Fenofibrate, F9 batch were subjected to stability study at temperature 40ºC± and relative humidity 75% ± for three months. After each month tablets were analyzed for hardness, friability, disintegration time, dissolution time and drug content. The results are as follows.

Table 17. Stability study of Mouth Dissolving Tablets of optimized batch

F9 at 40ºC ± 2ºC/75 % RH ± 5%

Parameters	Initial	After 1month	After 2months	After 3months
Hardness (kg/cm^3)	3.9±0.04	3.9±0.89	3.5±0.84	3.3±0.53
Friability (%)	0.61±0.01	0.66±0.76	0.71±0.7	0.751±0.97
Dintegration time (min.)	1.10±0.01	1.10±0.67	1.17±0.56	1.20±0.01

Content Uniformity (%)	99.51±1.32	99.21±0.12	98.73±1.32	97.32±0.32
Cumulative % Drug release	99.08±0.79	99.08±0.86	98.78±0.46	97.08±0.65

*Results are mean of 3 determinations

From the above table it is concluded that, the Mouth Dissolving Tablets of solid dispersion of Fenofibrate from tablet F9 batch are physically stable and retained their original properties when stored at 40ºc ± 2ºc/75 % RH ± 5% and after three months was no significant difference in disintegration time, cumulative % drug release, hardness, friability and drug content.

CONCLUSION

All the formulations of solid dispersions were successfully prepared and Fenofibrate tablets are prepared and evaluated for solubility and dissolution rate. The saturation solubility of drug was found to be more in the solid dispersions as compared to the phase solubility achieved in the presence of hydrophilic carriers in the dissolution media. This may be due to drug carrier interaction or change in property of drug in the solid dispersion formulations. Highest solubilizing power of Povidone towards Fenofibrate was shown by dissolution studies. From FTIR spectroscopy studies, it was concluded that there was no defined chemical interactions between Fenofibrate and Povidone. It can provide a promising way to enhance its solubility and dissolution rate.

In the present investigation we developed mouth dissolving tablets of fenofibrate by Solid Dispersion technique.The wetting time or simulated saliva penetration was observed to be very fast with batch F9 tablets. The total drug from the optimized batch was found to be released within the first ten minutes of dissolution study. These tablets rapidly dissolved (within 60-70 sec) in saliva. The prepared tablet gives benefit in terms of patient compliance, low dosing, rapid onset of action, increased bio-availability, low side effect and good stability which make these tablets popular as a dosage form for the treatment of hyperlipidemia.

ACKNOWLEDGMENT

The authors would like to thank Mylan Healthcare Pvt.Ltd Sinner, India for providing gift sample of fenofibrate. The authors also thank Dr. Ashok V. Bhosale, Principal, Shankarrao Ursal college of Pharmaceutical Sciences and Research Centre, Kharadi, Pune, India. for providing all the facilities and encouragement for the research work.

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