INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

ISSN: 2320-2831

*IJPAR |Vol.4 | Issue 4 | Oct- Dec -2015*
*Journal Home page: www.ijpar.com*

*Research article* *Open Access*

# Formulation and *invitro* evaluation of immediate release tablets of fenofibrate solid dispersions by different techniques.

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## ABSTRACT

The aim of the present research work, Fenofibrate a BCS class II Anti hyperlipidemic drug belongs to fibrate class was formulated as solid dispersions by using various hydrophilic carriers to enhance the solubility, dissolution rate and oral bioavailability. Solvent evaporation method, Fusion Method and Melt Solvent method are used to prepare solid dispersions of fenofibrate. Solid state characterization of solid dispersions is done by Differential Scanning Calorimetry, Fourier-Transform Infrared spectrometry and X-ray powder Diffraction studies, Scanning electron microscopy. The solid dispersions can be evaluated by in-vitro dissolution studies. To develop the solid oral dosage form (Tablets) with fenofibrate solid dispersions. To study the physical parameters of tablets prepared by direct compression, which includes hardness, friability, weight variation, and disintegration. To estimate the % drug content in the solid dispersions and the fabricated formulations. To evaluate the drug release from the tablets by in-vitro dissolution studies and to compare in-vitro dissolution profile of fabricated formulation with marketed formulation.

**Keywords**: Solid dispersion, Fenofibrate, BCS class II Anti-hyperlipidemic drug, Solvent evaporation method, Fusion Method and Melt Solvent method

## INTRODUCTION

### Solid dispersions

The formulation of hydrophobic drugs as solid dispersions is a significant area of research aimed at improving the dissolution and bioavailability of hydrophobic drugs. Solid dispersions consisting of two components in the solid state are referred to as binary systems. The two components are a water-soluble carrier and a hydrophobic drug dispersed in the carrier substance.[3]

### Definition of solid dispersions

Chiou and Riegelman[4] defined the term solid dispersion as 'the dispersion of one or more active Ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting- solvent method' While Corrigan[5] suggested the definition as 'product formed by converting a fluid drug-carrier combination to the solid state' several insoluble drugs have been shown to

improve their dissolution character when incorporated into solid dispersion. It releases the drug through different mechanisms, and the rate of release of drug to the surrounding fluid is mainly dependent on the type of solid dispersion formed.[6,7] Solid dispersion technique has been widely employed to improve the dissolution rate, solubility and oral adsorption of poorly water soluble drug's.[8,9]

## PREPARATION TECHNIQUES OF SOLID DISPERSIONS

### Solvent evaporation method

In this method, physical mixture of two components are dissolved in a common solvent and followed by the evaporation of solvent. The advantages of this method are low temperature requirement for the preparation of dispersion and thermal decomposition of drugs and carriers can be prevented. The higher cost of production, incomplete removal of solvent, adverse effects of solvent on the chemical stability of the drug and selection of common solvent are the drawbacks of this method.

### Melting method (Fusion method)

The physical mixture of drug and water- soluble carrier was heated to melt and the molten mixture was then cooled and solidified mass was crushed, pulverized and sieved. The melting point of a binary system depends on its composition and proper manipulation of drug carrier ratios. Decomposition should be avoided due to fusion time and rate of cooling.

### Kneading method

The physical mixture of drug and carrier were triturated using small quantity of organic solvent and water mixture, usually alcohol and water (1:1v/v).The slurry is kneaded for 45 minutes and dried at 45ºC. The dried mass is pulverized and sieved through sieve no 60 and the fraction was collected. The advantages of this method are low temperature requirement for solid dispersion preparation and usage of organic solvent is less. This method of preparation avoids thermal degradation of drug and employs less quantity of organic solvents.

### Melting solvent method

This method involves dissolving the drug in a suitable solvent and incorporation of the solution directly into the molten carrier. This method possesses the advantages of both solvent and melting methods.

### Supercritical fluid methods

Supercritical fluid methods are mostly applied with carbon dioxide ($CO_2$), which is used as either a solvent for drug and matrix or as an anti-solvent. This technique consists of dissolving the drug and the carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with $CO_2$. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel. This technique does not require the use of organic solvent and since $CO_2$ is considered environmentally friendly, this technique is referred to as 'solvent free'. This technique is known as Rapid Expansion of Supercritical Solution (RESS).

## AIM AND OBJECTIVE

The purpose of the investigation is to prepare Fenofibrate solid dispersion technique. It is mainly used to reduce cholesterol levels in patients at risk of cardiovascular disease. The specific objectives of the project are as follows:

- To design and develop Fenofibrate solid dispersions using indigenous Gelucire 50/13, Compitrol HD 5 and PEG 4000
- To evaluate tablets for their Fast dissolving properties.
- To conclude the ability of these indigenous Gelucire 50/13, Compitrol HD 5 and PEG 4000for Fast dissolving of Fenofibrate

## METHODOLOGY

### Construction of Standard Graph of Fenofibrate 0.75% SLS in water

### Preparation of stock solution

Accurately weighed amount of 10 mg fenofibrate was transferred into a 10ml volumetric flask. 5 mL of methanol was added to dissolve the drug and volume was made up to 10 mL with 0.75% SLS in water. The resulted solution had the concentration of 1mg/ml which was labelled as 'stock'.

### Preparation of working standard solution

From this stock solution 1ml was taken and diluted to 10 mL with 0.75% SLS in water which has given the solution having the concentration of 100 mcg/mL.

### Preparation of serial dilutions for standard calibration curve

Necessary dilutions were made by using this second solution to give the different concentrations of fenofibrate (5-25 mcg/mL) solutions. The absorbances of above solutions were recorded at $\lambda_{max}$ (286 nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

## FORMULATION OF SOLID DISPERSIONS

### Solid dispersion of fenofibrate with gelucire 50/13, compitrol hd 5 and polyethylene glycol 4000 (peg 4000)

### Methods of Preparation of Solid Dispersion

Solid dispersions were prepared by different methods like solvent evaporation, fusion method and Melt solvent method.

### Solvent evaporation method

Fenofibrate and each of water soluble carrier gelucire 50/13, compitrol hd 5 and polyethylene glycol 4000 (peg 4000) were weighed accurately in various ratios (1:1, 1:2 and 1:3) and transferred to beaker containing sufficient quantity of acetone to dissolve. The solvent was evaporated at room temperature. The resulting solid dispersion was stored for 24 hrs in a desiccator to congeal. Finally, dispersion were passed through sieve no.85 and stored in desiccator till further use.

### Fusion Method

Each of water soluble carrier gelucire 50/13, compitrol hd 5 and polyethylene glycol 4000 (peg 4000) were weighed accurately in various ratios (1:1, 1:2 and 1:3) and melted in a porcelain dish at 80-85ºC and to this calculated amount of fenofibrate was added with thorough mixing for 1-2 minutes followed by quick cooling. The dried mass was then pulverized by passing through sieve no.85 and stored in a dessicator until used for further studies. Solid dispersions were prepared using compositions as given in Table

### Melt Solvent method

It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of carriers which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight.

### Preparation of tablets of fenofibrate solid dispersion

The Fenofibrate solid dispersion containing 67mg Fenofibrate were prepared.

### Manufacturing Procedure

- Lactose monohydrate, Super disintegrants, sodium lauryl Sulphate were weighed and sifted through 40 mesh.
- To the above blend Fenofibrate solid dispersion was added and sifted through 18 mesh.
- The sifted material was placed in cantabin blender and mixed for 8, 10, 12 min.
- Starch was dissolved in purified water and above was granulated
- The wet mass passed through Sieve no 12 and dried in tray dryer at $60^0$C.
- The dried granules were passed through Sieve no 18.
- Remaining part of super disintegrants, talc and aerosol were weighed and sifted through Sieve no 40 and mixed with the granulated blend.
- Magnesium Stearate were weighed and sifted through Sieve no 40.
- To the dried granules lubricated blend was added and placed in cantabin blender.
- The lubricated blend was compressed using 10 mm round punches.

# RESULTS
# PREFORMULATION STUDIES
## Physical Appearance
The physical appearance was done by visual observation and found that Fenofibrate was a white to off white crystalline powder.

**Table no 1. Sieve analysis**

| Sieve no. | %retain | %cumulative retain |
|---|---|---|
| 40 | 0.7 | 0.7 |
| 60 | 16 | 16.7 |
| 80 | 28 | 44.7 |
| 100 | 14 | 58.7 |
| Base plate | 41.3 | 100 |

**Table no. 2 Characteristics of choline fenofibrate)**

| S.No. | TEST | SPECIFICATION | RESULT |
|---|---|---|---|
| 1 | Description | white to off white crystalline powder | white to off white crystalline powder |
| 2 | Solubility | Soluble in water and slightly soluble in Methanol | Complies |
| 3 | Water Content (by Karl-Fisher) | Should be between 3.2% and 5.9% | 4.6% w/w |
| 4 | LOD | by IR moisture analyzer, at $105^0$C | 1.30 % w/w |
| 5 | Bulk density<br>Tapped density<br>Haussner's Ratio<br>Carr's/Compressibility Index (%) | | 0.23 gm/ml<br>0.26 gm/ml<br>1.13<br>13 |
| 6 | Melting Point | 79 - 83 $^o$C | 81.5$^o$C |
| 7 | AssayAnhydrousBasis (Potentiometric) | <98% and not more than 102% w/w | 99.6%w/w |

**Calibration curve of Fenofibrate in 0.75% SLS**

Wavelength of maximum absorption: 286 nm.

Table no 3: standard curve of Fenofibrate in 0.75% SLS solution at λmax 286nm

| Concentration (µg/mL) | Absorbance |
|---|---|
| 0 | 0 |
| 5 | 0.14 |
| 10 | 0.301 |
| 15 | 0.449 |
| 20 | 0.605 |
| 25 | 0.753 |

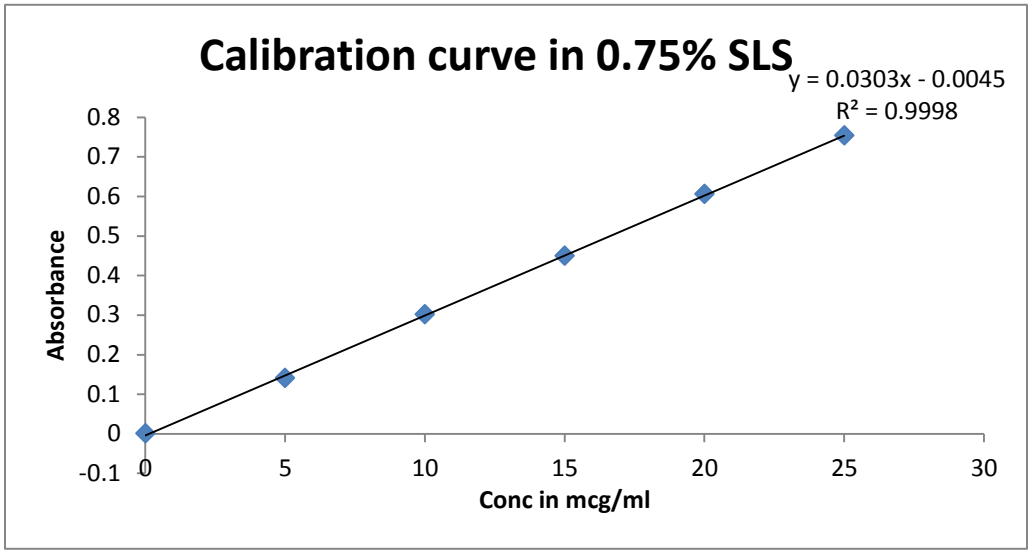


**Fig No 1: standard curve of Fenofibrate in 0.75% SLS**

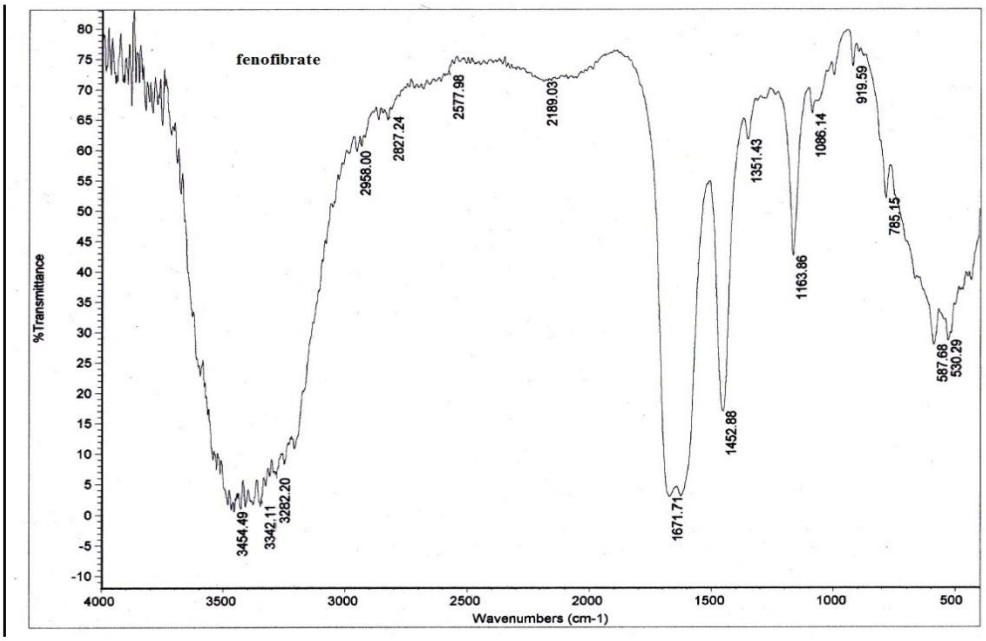


**Fig No 2: FENOFIBRATE PURE DRUG**

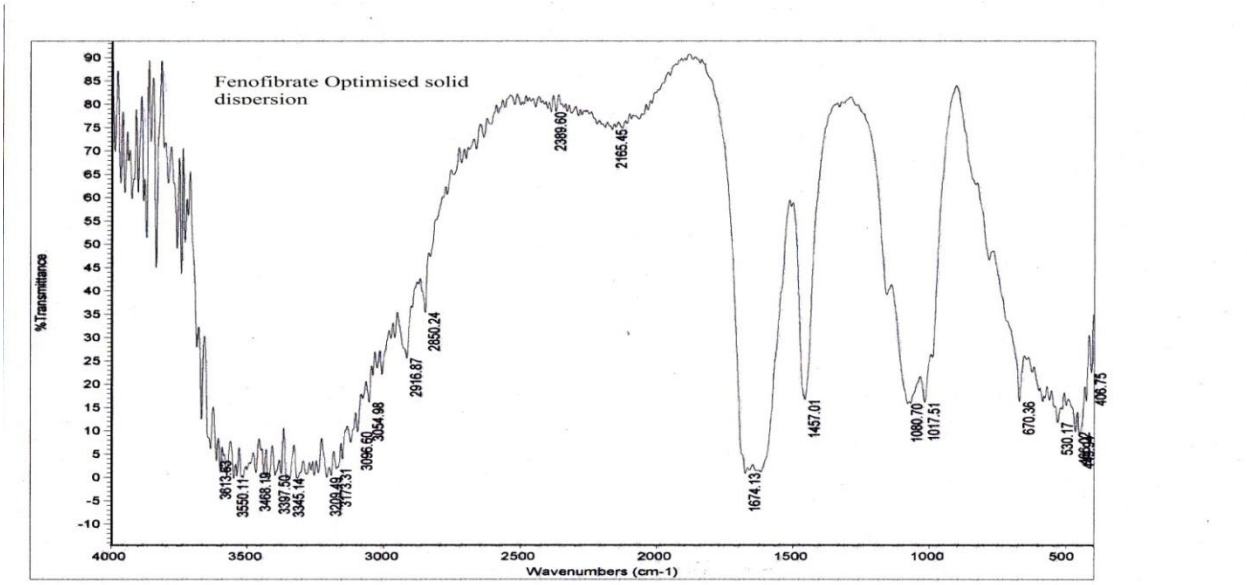


**Fig No 3: FENOFIBRATE SOLID DISPERSIONS**

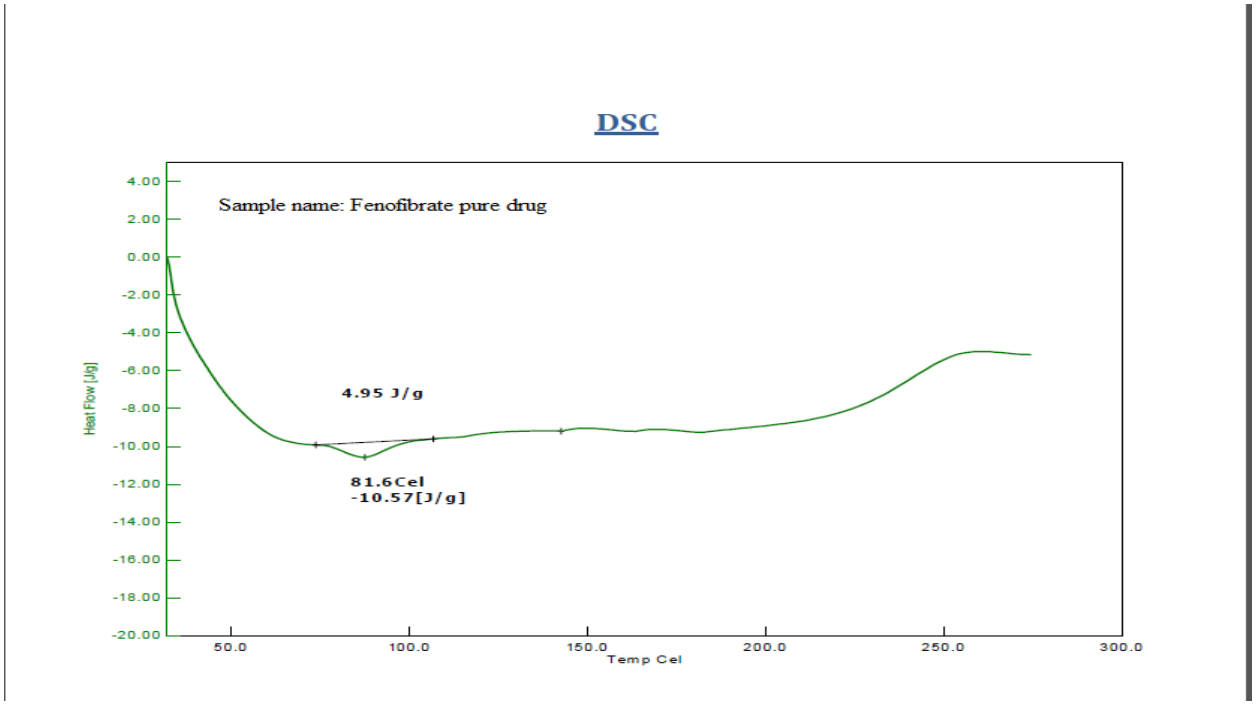


**Fig No 4: FENOFIBRATE PURE DRUG**

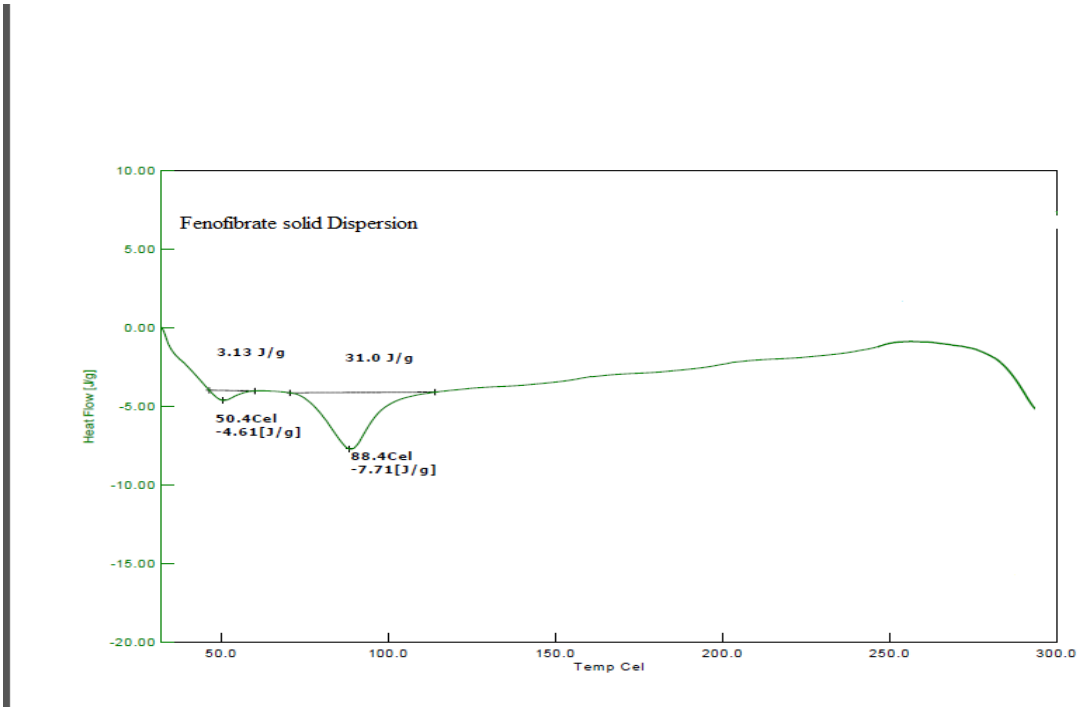


**Fig No 5: Fenofibrate solid dispersions**

**Solid dispersion (Table no 4)**

Bulk density, Tapped density, % Compressibility index, Hausner ratio (Precompression studies) of Solid dispersions

| Formulation code | Tapped density (gm /ml) | Bulk density (gm/ml) | Hausner ratio | Carr's index (%) | Angle of repose | Flow property |
|---|---|---|---|---|---|---|
| **SD1** | 0.252±0.023 | 0.233±0.022 | 1.085±0.12 | 8.48±0.45 | $31.25^0$ | Good |
| **SD2** | 0.264±0.024 | 0.241±0.017 | 1.094±0.14 | 9.41±0.56 | $31.55^0$ | Good |
| **SD3** | 0.267±0.025 | 0.245±0.017 | 1.089±0.14 | 8.89±0.67 | $32.15^0$ | Good |
| **SD4** | 0.270±0.026 | 0.246±0.019 | 1.096±0.15 | 9.64±0.36 | $32.19^0$ | Good |
| **SD5** | 0.265±0.025 | 0.241±0.021 | 1.098±0.14 | 9.81±0.45 | $32.38^0$ | Good |
| **SD6** | 0.267±0.025 | 0.248±0.022 | 1.076±0.11 | 7.63±0.19 | $33.41^0$ | Good |
| **SD7** | 0.265±0.025 | 0.241±0.025 | 1.098±0.12 | 9.81±0.27 | $34.41^0$ | Good |
| **SD8** | 0.270±0.026 | 0.246±0.023 | 1.096±0.11 | 9.64±0.23 | $32.41^0$ | Good |
| **SD9** | 0.263±0.025 | 0.251±0.024 | 1.049±0.09 | 4.88±0.24 | $33.51^0$ | Good |

| | | | | | | |
|---|---|---|---|---|---|---|
| **SD10** | 0.279±0.025 | 0.229±0.020 | 1.220±0.08 | 22.02±0.45 | $34.12^0$ | Good |
| **SD11** | 0.274±0.026 | 0.238±0.022 | 1.152±0.12 | 15.20±0.28 | $33.41^0$ | Good |
| **SD12** | 0.306±0.028 | 0.270±0.026 | 1.135±0.14 | 13.51±0.26 | $34.41^0$ | Good |

The preformulation studies showed a good flow property for formulation trials where as the pure drug showed very poor flow property it clearly indicated that the flow property has been improved by the addition of magnesium stearate as lubricant.

**Table no. 5 Solubility studies:**

| **Formulations** | **Solubility 0.75% SLS water (mcg/ml)** | | | **Avg** | **S.D** |
|---|---|---|---|---|---|
| | **1** | 2 | 3 | | |
| **SEG1** | 156 | 148 | 141 | 148 | 6.13 |
| **SEG2** | 192 | 182 | 173 | 183 | 7.77 |
| **SEG3** | 205 | 195 | 185 | 195 | 8.16 |
| **MFG1** | 189 | 180 | 171 | 180 | 7.35 |
| **MFG2** | 204 | 194 | 184 | 194 | 8.16 |
| **MFG3** | 218 | 217 | 217 | 217.3 | 8.58 |
| **MEG1** | 170.1 | 162 | 153.9 | 162 | 6.615 |
| **MEG2** | 183.6 | 174.6 | 165.6 | 174.6 | 7.344 |
| **MEG3** | 196.2 | 195.3 | 195.3 | 195.57 | 7.722 |
| **SEC1** | 100 | 95 | 90 | 95 | 4.08 |
| **SEC2** | 120 | 114 | 108 | 114 | 4.90 |
| **SEC3** | 140 | 133 | 126 | 133 | 5.72 |
| **MFC1** | 90 | 86 | 81 | 86 | 3.69 |
| **MFC2** | 150 | 143 | 135 | 143 | 6.13 |
| **MFC3** | 140 | 133 | 126 | 133 | 5.72 |
| **MEC1** | 140.4 | 133.2 | 126.9 | 133.5 | 5.52 |
| **MEC2** | 172.8 | 163.8 | 155.7 | 164.7 | 6.993 |
| **MEC3** | 184.5 | 175.5 | 166.5 | 175.5 | 7.344 |
| **SEP1** | 90 | 85.5 | 81 | 85.5 | 3.672 |
| **SEP2** | 108 | 102.6 | 97.2 | 102.6 | 4.41 |
| **SEP3** | 126 | 119.7 | 113.4 | 119.7 | 5.148 |
| **MFP1** | 81 | 77.4 | 72.9 | 77.4 | 3.321 |
| **MFP2** | 135 | 128.7 | 121.5 | 128.7 | 5.517 |
| **MFP3** | 126 | 119.7 | 113.4 | 119.7 | 5.148 |
| **MEP1** | 126.36 | 119.88 | 114.21 | 120.15 | 4.96389 |
| **MEP2** | 155.52 | 147.42 | 140.13 | 148.23 | 6.2937 |
| **MEP3** | 166.05 | 157.95 | 149.85 | 157.95 | 6.6096 |
| **Pure drug** | 67 | 68 | 66 | 67 | 1.0 |

**Table no. 6 Post compression studies of Solid dispersion Formulation:**

| Formulation code | Weight variation | Hardness ( kg/cm$^2$) | Friabilty (%) | Thickness (mm) | Content uniformity | Disintegration Time (min) |
|---|---|---|---|---|---|---|
| **SD1** | 438±0.009 | 6.2±0.52 | 0.18±0.45 | 2.6±0.018 | 100.1±0.05 | 4mins |
| **SD2** | 442±0.015 | 6.3±0.51 | 0.21±0.46 | 2.6±0.019 | 98.96±0.04 | 3 mins 30 secs |
| **SD3** | 440±0.023 | 6.1±0.50 | 0.16±0.43 | 2.7±0.020 | 99.2±0.08 | 3 mins30 secs |
| **SD4** | 441±0.012 | 6.2±0.52 | 0.24±0.45 | 2.75±0.021 | 99.2±0.08 | 3 mins |
| **SD5** | 439±0.012 | 5.8±0.49 | 0.11±0.46 | 2.6±0.020 | 98.5±0.05 | 2 mins 30 secs |
| **SD6** | 443±0.013 | 6.0±0.51 | 0.25±0.55 | 2.62±0.022 | 98.5±0.05 | 1 mins |
| **SD7** | 440±0.023 | 6.1±0.52 | 0.15±0.43 | 2.6±0.024 | 101.5±0.05 | 1 mins |
| **SD8** | 441±0.045 | 6.2±0.53 | 0.16±0.34 | 2.56±0.018 | 99.6±0.04 | 1 mins 15 secs |
| **SD9** | 442±0.034 | 6.1±0.51 | 0.14±0.32 | 2.59±0.019 | 99.2±0.08 | 1 mins 15 secs |
| **SD10** | 443±0.034 | 6.0±0.50 | 0.21±0.41 | 2.56±0.016 | 98.9±0.01 | 1 min |
| **SD11** | 446±0.116 | 6.3±0.59 | 0.12±0.30 | 2.87±0.029 | 100.2±0.08 | 1 min |
| **SD12** | 445±0.012 | 6.3±0.59 | 0.15± | 2.65±0.026 | 100.1±0.09 | 14 mins 25 secs |

The weight variation ranges from 438±0.009 to 446±0.116 and was found to be less than 5% as per U.S.P guidelines. The Hardness Ranges from 5.8±0.49 to 6.3±0.59 and was found to be satisfactory. The Thickness ranges from 2.56±0.016 to 2.87±0.029, the friability was found to be less than 1% and was found to be within the limits. As the disintegrant concentration increases the disintegration time decreases and percentage of drug release rate increases. The formulation SD11 showed less disintegration time of 1min and showed highest percent of drug release in 20min.

**Table no. 7 *In -vitro* drug release study**

Paddle method Dissolution data of tablets formulations of Fenofibrate by Paddle method (USP II) are reported.
Dissolution Values of **Solid dispersion formulation**

| Time in min | SD1 | SD2 | SD3 | SD4 | SD5 | SD6 | SD7 | SD8 | SD9 | SD10 | SD11 | SD12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **5** | 8.064 ±0.1 | 12.6 ±0.2 | 28.98 ±0.1 | 39.06 ±0.1 | 15.12 ±0.6 | 16.38 ±0.2 | 12.3± 0.7 | 16.9± 0.1 | 34.02 ±0.8 | 45.36 ±0.7 | 47.88 ±0.2 | 2.52±0. 21 |
| 10 | 22.68 ±0.2 | 28.98 ±0.1 | 52.92 ±0.4 | 64.26 ±0.2 | 27.72 ±0.8 | 31.5± 0.1 | 22.9± 0.1 | 32.1± 0.9 | 66.78 ±0.2 | 60.56 ±0.5 | 68.04 ±0.9 | 16.38±0 .34 |
| 15 | 31.5 ±0.1 | 37.8 ±0.2 | 61.74 ±0.3 | 75.6± 0.8 | 39.06 ±0.4 | 42.84 ±0.6 | 36.4± 0.6 | 42.4± 0.6 | 78.12 ±0.4 | 76.94 ±0.1 | 88.2± 0.8 | 30.24±0 .03 |
| 20 | 40.32 ±0.3 | 46.62 ±0.3 | 76.86 ±0.4 | 83.98 ±0.7 | 45.36 ±0.4 | 52.92 ±0.2 | 49.2± 0.8 | 52.6± 0.4 | 94.5± 0.5 | 91.8± 0.2 | 100.8 ±0.2 | 36.54±0 .056 |
| 30 | 49.14 ±0.3 | 57.96 ±0.2 | 88.2± 0.2 | 91.5± 0.8 | 55.44 ±0.6 | 64.26 ±0.4 | 55.4± 0.6 | 64.2± 0.8 | 100.8 ±0.2 | 100.9 ±0.1 | 0 | 45.36±0 .53 |
| 45 | 55.44 | 65.52 | 98.28 | 100.4 | 66.78 | 76.86 | 68.9± | 81.8± | 0 | 0 | 0 | 52.92±0 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ±0.2 | ±0.2 | ±0.2 | ±0.6 | ±0.2 | ±0.2 | 0.1 | 0.2 | | | | .36 |
| 60 | 75.52 | 81.9± | 100.5 | 0 | 84.42 | 90.72 | 76.2± | 88.6± | 0 | 0 | **0** | 80.48±0 |
| | ±0.3 | 0.1 | ±0.5 | | ±0.6 | ±0.3 | 0.8 | 0.4 | | | | .32 |

We selected **SD – 11** as the best formulation as it showed total drug release with in 20 min than all other formulations.

## SUMMARY AND CONCLUSION

The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility. Solid dispersions is the techniques are the most attractive processes to improve solubility of poorly soluble drugs. The concept of formulating fast dissolving tablets using super disintegrants offers a suitable and practical approach of faster disintegration and dissolution characteristics. Fenofibrate is a Hipolipidemic agent which reduces both cholesterol and triglycerides in the blood. It is mainly used to reduce cholesterol levels in patients at risk of cardiovascular disease. Fenofibrate is a lipid regulating agent indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-C,Triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia. Here the solubility of Fenofibrate is enhanced by solid dispersions with Gelucire 50/13, Compitrol HD 5 and PEG 4000. Then the formed solid dispersions is characterized and evaluated by drug content and *IN VITRO* dissolution studies. As the disintegrant concentration increases the disintegration time decreases and percentage of drug release rate increases. The formulation SD11 showed less disintegration time of 1min and showed highest percent of drug release in 20min. SD – 11 as the best formulation as it showed total drug release with in 20 min than all other formulations. There was no significant change in physical and chemical properties of the conventional tablets prepared from Solid dispersion of formulation after 3 Months.

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