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FORMULATION AND CHARACTERIZATION OF SOLID DISPERSIONS OF A POORLY SOLUBLE FENOFIBRATE

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Keywords:
Fenofibrate, Bioavailability, Solid dispersion, Preformulation parameters, Dissolution enhancement, carriers, solubility.

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ABSTRACT: Solid dispersion is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs. The solid dispersions based on the concept that the drug is dispersed in an inert water-soluble carrier at solid state. Several water soluble carriers such as methyl cellulose, urea, lactose, citric acid, polyvinyl pyrrolidone and polyethylene glycols 4000 and 6000 are used as carriers for solid dispersion. Thus the solid dispersion technique can be successfully used for the improvement of dissolution of Fenofibrate. Various solvents, carrier materials, diluents, disintegrating agents, lubricants has been used for the preparation of solid dispersion of fenofibrate. Over the years, a variety of solubilization techniques have been studied and widely used, by many estimates up to 40 per cent of new chemical entities discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. The various techniques are available for enhancement of solubility. Solid dispersion is one of the most promising approach for solubility enhancement. Different methods are also been used for preparation of solid dispersions such as Melting method, Solvent method, Melting solvent method (melt evaporation), Melt extrusion method, Lyophilisation Technique, Melt Agglomeration Process, The Use Of Surfactant, Electrospinning and Super Critical Fluid (SCF) Technology. Preformulation and evaluation parameters in this study explain about the flowability and acceptability of the prepared formulations. DSC studies explain about the compatibility between the different excipients used in the formulations.

INTRODUCTION: Immediate release oral dosage forms are most widely used drug delivery systems available. These products are designed to disintegrate in the stomach followed by their dissolution in the fluids of the gastrointestinal tract. Dissolution of the drug substance under physio-logical conditions is essential for its systemic absorption.

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For this reason dissolution testing is typically performed on solid dosage forms to measure the drug release form the drug product as a test for product quality assurance/product performance and to determine the compliance with dissolution requirements when stated in the individual monograph. In limited number of cases, an *in vitro – in vivo* correlation is established between the drug release and drug product absorption necessary for therapeutic effect. Disintegration test is also a standardized test and is primarily used as a quality assurance tool to confirm complete disintegration of solid oral dosage forms within the prescribed

time when placed in a liquid medium under the experimental conditions [1, 2, 3].

Solid Dispersion: Dispersion of the drug as very fine particles will increase the surface area available for dissolution. According to the classical Noyes-Whitney equation this will increase the dissolution rate. Particle size reduction may go to the nano-scale. However, even this size reduction will not lead to concentrations above the maximum solubility of the drug in the intestinal fluids [4]. Alternatively, solid dispersions can be used to increase the dissolution rate of poorly soluble drug and they have proven to increase the amount of dissolved drug at the absorption site sometimes to supersaturated concentrations and consequently improve the bioavailability [5]. Solid dispersions are investigated in many studies because they are highly versatile in their application. They can form the basis of products applied for various routes of administration and for various dosage forms, including the most popular dosage form the tablet (**table 1**) [6-10].

Advantages of Solid Dispersions:

- Solid dispersions of a drug in solid state are helpful in stabilizing unstable of drug.
- Many advantages of solid dispersions are derived from their rapid dissolution rate.
- Solid dispersions are thermodynamically more active form of a drug and directly influences diffusion and release rate.
- The dose of drug that is given in solid dispersion form could be decreased; for example, the dose of reserpine spironolactone can be reduced to half by incorporating the drug in a solid dispersion form [11-15].
- Solid dispersion of drug in carriers of low solubility offers the potential for sustained release of drug.
- Cell toxicity of Acyclovir can be decreased by solid dispersion method.
- The ulcerogenic activity of NSAIDS can be decreased by solid dispersion method.
- An increased diffusion of steroid from the ointment was obtained, example Prednisolone urea ointment base.
- Solid dispersion can be used to solidify liquid drug for e.g. Clofibrate and benzyl benzoate.

Disadvantages of Solid Dispersions:

- There are chances of changes during storage of amorphous or molecularly dispersed drug.
- High humidity induced changes in solid dispersions were observed if chosen carriers are water soluble, hygroscopic and moisture sensitive that results in decreased dissolution rates from many dispersions including Diazepam-PEG 6000, Nifidepine and Indomethacin-PVP.
- Tackiness and decommissions during preparation and formulation.
- The oral administration of solid dispersions without concomitant reduction in dose may result in higher incidence of adverse effect e.g. Ulceration with Indomethacin -PEG 6000 dispersion [16].

PREFORMULATION STUDIES:

1. Solubility:
2. Flow Properties:
   - Bulk density
   - Tapped density
   - % Compressibility
   - Hausner's ratio
3. Particle size distribution
4. Hygroscopic studies
5. Fenofibrate Excipient Compatibility studies

Evaluation studies of tablets

1. Dissolution studies [21-27]

Materials: Fenofibrate (Anti-Cholesteramine agent) gift sample from Aurobindo Chemicals Pvt. Ltd, Polyethylene glycol 6000, Polyethylene glycol 400, Cremophore EL, Miglyol, Sugar spheres Celpheres are collected from S.D. Fine chemicals, Lactose monohydrate (Flowlac 100), Pharmatose Microcrystalline cellulose, Pre-gelatinized starch, *Ac-di-sol* (Crosscarmellose sodium) are procured from Hi Media labs Pvt Ltd, Colloidal silicon

dioxide, Magnesium stearate, Isopropyl alcohol are collected from Micro labs.

Classification of Solid Dispersions:

TABLE 1: CLASSIFICATION OF SOLID DISPERSIONS: [18-20]

	Type of solid dispersion	Matrix	Drug	Remark
1	Eutectic	C	C	The first type of solid dispersion prepared.
2	Amorphous precipitations in crystalline matrix.	C	A	Rarely encountered.
	Solid solutions			
	Continuous solid solutions	C	M	Miscible at all composition, never prepared.
	Discontinuous solid solutions	C	M	Partially miscible, 2 drugs even though drug is molecularly dispersed.
3	Substitutional solid solutions	C	M	Molecular diameter of drug (solute) differs less than15% from matrix (solvent diameter). In that case the drug and matrix are substitutional. Can be continuous or discontinuous, when discontinuous; 2 phases though drug is molecularly dispersed.
	Interstitial solid solutions	C	M	Molecular diameter of drug (solute) less than 59% from matrix (solvent diameter). Usually limited miscibility, discontinuous. Example; drug in helical interstitial spaces of PEG.
4	Glass suspensions.	A	C	Particle size of disperse phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix.
5	Glass suspensions.	A	A	Particle size of disperse phase dependent on cooling/ evaporation rate, many solid dispersion are of this type.
6	Glass solutions.	A	M	Requires miscibility/solid solubility, complex formation or upon fast cooling/evaporation during preparation. Many recent examples especially with PVP.
	Other related designs			
7	Complex formation	C/M	M	Drug and matrix strongly interact and form complexes in aqueous environment. Ex; cyclodextrin and solid surfactants.
8	Monotectics	C	C	Same as eutectics but eutectics melting convergent with pure material, for completely non-interacting system.
9	Co-precipitates	-	-	Prepared by addition of non-solvents to solution of drug and matrix.
10	Co-evaporates	-	-	Prepared by vacuum drying, spray drying, freeze drying and spray freeze drying, many examples.

A: Amorphous state, C: Crystalline state, M: Drug molecularly dispersed throughout the matrix.

FORMULATION METHODS: Preparation of solid dispersion of Fenofibrate by Solvent Evaporation method using fluid-bed coating technique as shown in **fig. 1.**

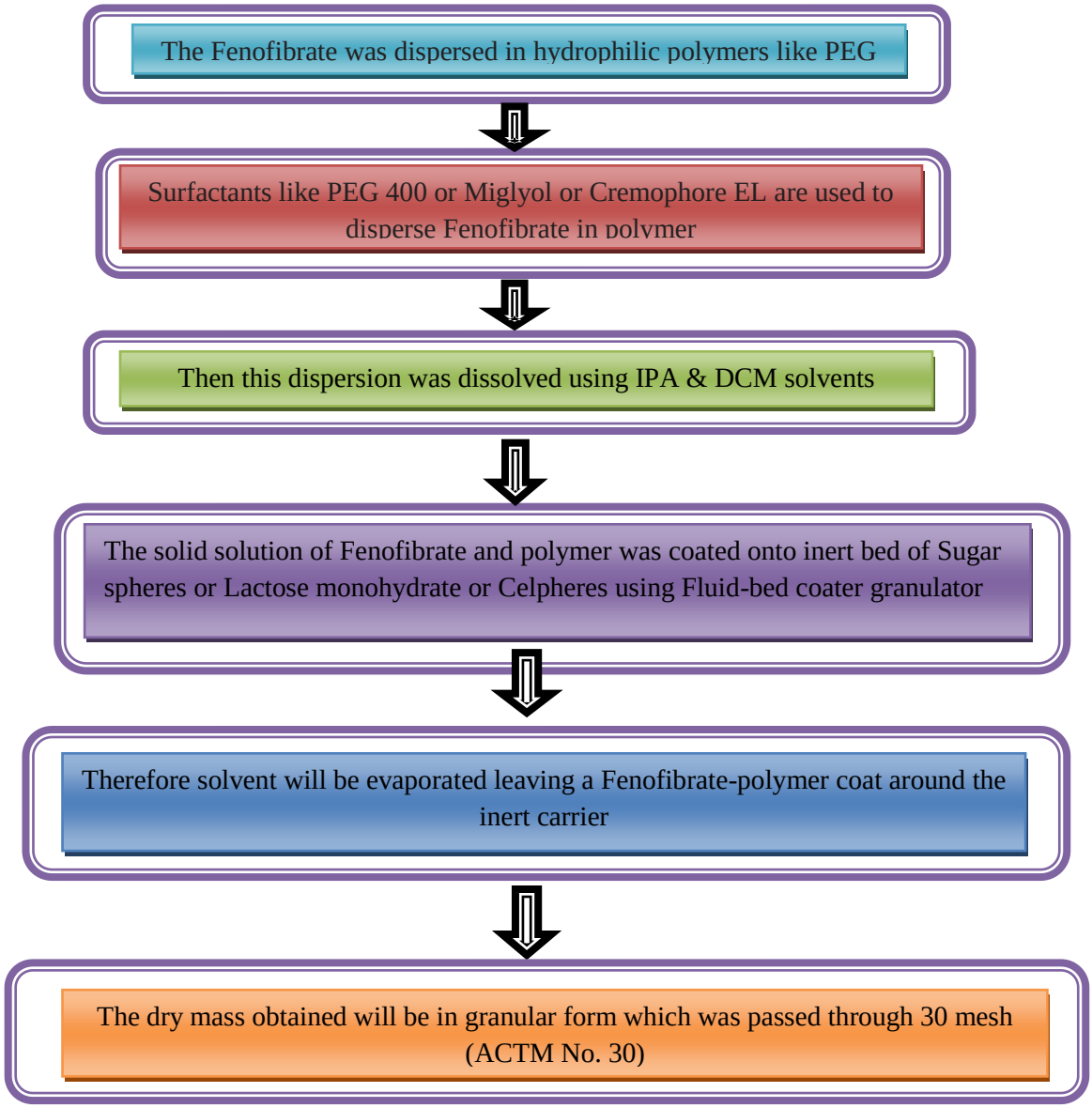

FIGURE 1: PREPARATION OF SOLID DISPERSION OF FENOFIBRATE BY SOLVENT EVAPORATION METHOD USING FLUID-BED COATING TECHNIQUE

FORMULATION DEVELOPMENT:

1. **F1:** Bottom spraying of Fenofibrate solution on sugar spheres lead to lump formation due to oily nature of surfactant Cremophore EL. Process was not satisfactory. Trial with different surfactant was planned.
2. **F2:** Top spraying of Fenofibrate solution on lactose monohydrate lead to bed dampening and fluidization problem because of oily nature of surfactant Miglyol. Process was not satisfactory. Trial with different polymer and surfactant was planned.
3. **F3:** Bottom spraying of Fenofibrate solution on celpheres lead to lump formation. The process was not satisfactory. Granulation was planned by top spraying the Fenofibrate solution on lactose monohydrate.
4. **F4:** Granulation process was satisfactory. But heavy sticking occurred during compression

because of presence of large quantity of PEG in the formulation.

5. **F5:** To address the sticking issue, diluent was incorporated in the extragranular part and tablet weight was increased along with increased quantity of lubricant. Slight sticking was observed during compression. Fenofibrate release was negligible with compared to innovator.
6. **F6:** To improve the Fenofibrate release, superdisintegrant was incorporated in the extragranular part and water insoluble diluents (MCC and PGS) being used to address the sticking issue. Dissolution was faster compared to the innovator.
7. **F7:** To get the desired dissolution profile, superdisintegration concentration was reduced in the extragranular part but not much difference in the Fenofibrate release was achieved.
8. **F8:** To achieve the desired release profile, polymer concentration was decreased. The Fenofibrate release was faster at initial stage compared to the innovator.
9. **F9:** The disintegrant concentration was decreased in the extragranular part to achieve the desired profile. Dissolution was comparable to that of innovator.
10. **F10:** Reproducible batch was taken to confirm the reproducibility of batch F9 as shown in **table 2** and proto-type formulation in **table 3**.

TABLE 2: COMPOSITION OF SOILD DISPERSION OF FENOFIBRATE

S. No.	Ingredients	Ingredients (mg/tablet)									
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Fenofibrate	120	120	120	120	120	120	120	120	120	120
2	PEG 6000	156	-	156	156	156	156	156	120	120	120
3	Cremophore EL	67	-	-	-	-	-	-	-	-	-
4	Miglyol 812	-	120	-	-	-	-	-	-	-	-
5	PEG 400	-	-	30	30	30	30	30	24	24	24
6	DCM	1150	158	310	310	310	310	310	310	310	310
7	IPA	682	300	200	200	200	200	200	200	200	200
8	Sugar spheres	300	-	-	-	-	-	-	-	-	-
9	Lactose monohydrate	-	384	-	300	300	300	300	366	366	366
10	Celpheres	-	-	300	-	-	-	-	-	-	-
	Extra Granular										
1	Pharmatose 200M	-	-	-	-	344	-	-	-	-	-
2	Pregelatinized Starch (Lycatab)	-	-	-	-	-	134	134	134	134	135
3	Ac-di-sol (CCS)	-	-	-	-	-	100	50	100	50	51
4	MCC pH 102	-	-	-	-	-	130	180	106	156	156
5	Aerosil 200	-	-	-	-	-	10	10	10	10	12
6	Magnesium stearate	-	-	-	14	20	20	20	20	20	18
	Total			-	650	1000	1000	1000	1000	1000	1002
Ratio of Fenofibrate to polymer		1:1.3	-	1:1.3	1:1.3	1:1.3	1:1.3	1:1.3	1:1	1:1	1:1

TABLE 3: PROTOTYPE FORMULATION (F10)

S. No.	Name of the ingredients	Category
1	Fenofibrate (Anti-Cholesteramine agent)	Active excipient
2.	Polyethylene glycol 6000	Polymer (hydrophilic carrier)
3	PEG 400	Wetting agent
4.	Lactose monohydrate (Flowlac 100)	Inert carrier
5.	Microcrystalline cellulose (pH 102)	Diluent
6.	Pregelatinized Starch	Diluent
7.	*Ac-di-sol* (Crosscarmellose sodium)	Disintegrant
8.	Aerosil (colloidal silicon dioxide)	Glidant
9.	Magnesium stearate	Lubricant
10.	Isopropyl alcohol	Solvent
11.	Dichloromethane	Solvent

RESULTS AND DISCUSSION:

Solubility Studies: Solubility studies were done in different buffers to select the dissolution medium for the dissolution studies of the solid dispersions as shown in **table 4**.

TABLE 4: SOLUBILITY STUDIES

Solubility in different media (µg/ml)		
Solvent	**Pure Fenofibrate**	**Solid dispersion**
Water	0.2568	2.621
0.1N HCL	0.3637	3.521
pH 4.5 Acetate buffer	0.2568	2.124
pH 6.8 Phosphate buffer	0.1284	0.834
pH 7.5 Phosphate buffer	0.1926	1.221

Flow characterization parameters: The flow indices show that Fenofibrate has very poor flow as shown in **table 5**.

TABLE 5: FLOW PROPERTIES OF FENOFIBRATE

Bulk density (g/ml)	0.27
Tapped density (g/ml)	0.49
Compressibility Index (%)	1.82
Hausner's Ratio	44.9

Particle size distribution: The particle size distribution data of Fenofibrate was reported as less than 11.7 microns.

Hygroscopic studies: The hygroscopic study of Fenofibrate was done under following temp. & humidity conditions as shown in **table 6.** The Hygroscopicity study of Fenofibrate Fenofibrate indicates that Fenofibrate is non-hygroscopic in nature as the % weight increase in the samples at the study is less than 0.2%.

TABLE 6: HYGROSCOPICITY DATA

Time Interval	**% Weight Change**		
	33% RH	**53% RH**	**75% RH**
Day 1	0.00	0.0	0.0
Day 2	0.00	0.03	0.0
Day 4	0.00	0.03	0.01
Equilibrium RH			
Day 0		0.415	
Day 4	0.479	0.523	0.529
Remarks		Non-hygroscopic	

Fenofibrate - excipients compatibility studies: The results of Fenofibrate excipients compatibility studies suggest that there was no change in the physical appearance of mixtures when stored at 40°C ± 2°C / 75% ± 5% RH for 1 month.

Physical observations of Excipients Compatibility Study: The results of Fenofibrate excipients compatibility studies as shown in **table 7** suggest that there was no change in the physical appearance of mixtures when stored at 40°C ± 2°C / 75% ± 5% RH for 1 month.

TABLE 7: API – EXCIPIENTS COMPATIBILITY STUDY PHYSICAL OBSERVATIONS (STORAGE CONDITION: 40°C/75%RH)

S. No.	**Binary mixture (Ratio)**	**Observations**		
		Initial	**After 15 Days**	**After 30 Days**
1	Fenofibrate	White powder to off-white powder	White powder to off-white powder	White powder to off-white powder
2	Fenofibrate: Sucrose (1:10)	White powder to off-white powder	White powder to off-white powder	White powder to off-white powder
3	Fenofibrate: MCC pH 101 (1:10)	White powder to off-white powder	White powder to off-white powder	White powder to off-white powder

4	Fenofibrate: Lactose (1:10)	White powder to off-white powder	White powder to off-white powder	White powder to off-white powder
5	Fenofibrate: Pre-Gelatinized starch (1:10)	White powder to off-white powder	White powder to off-white powder	White powder to off-white powder
6	Fenofibrate: Crosscarmellose sodium(1:1)	White powder to off-white powder	White powder to off-white powder	White powder to off-white powder
7	Fenofibrate: Magnesium stearate (1:0.5)	White powder to off-white powder	White powder to off-white powder	White powder to off-white powder
8	Fenofibrate: Colloidal silicon dioxide (1:0.5)	White powder to off-white powder	White powder to off-white powder	White powder to off-white powder
9	Fenofibrate: PEG 6000(1:10)	White powder to off-white powder	White powder to off-white powder	White powder to off-white powder
10	Fenofibrate: PEG 400(1:0.5)	Clear viscous liquid	Clear viscous liquid	Clear viscous liquid
11	Fenofibrate: Cremophore EL (1:0.5)	White powder to off-white waxy liquid	White powder to off-white waxy liquid	White powder to off-white waxy liquid
12	Fenofibrate: Miglyol 812(1:0.5)	Hazy oily liquid	Hazy oily liquid	Hazy oily liquid

Evaluation of Tablets: (Table 8)

TABLE 8: PHYSICAL EVALUATION

S. No.	Physical parameter	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F8	F9	F10
1	**Weight variation (%)**					0.23	0.27	0.19	0.22	0.21	0.15
2	**Hardness (Kp)**					6.6-7.7	7.6-8.6	7.6-9.0	13.7-14.5	11.2-14.1	10.2-11.5
3	**Thickness (mm)**	N/A	N/A	N/A	N/A	6.31-6.35	6.28-6.30	6.34-6.37	6.46-6.50	6.43-6.44	6.51-6.54
4	**Friability (%)**					0.045	0.042	0.042	0.042	0.033	0.04
5	**Disintegration time**					22-25 min	11-12 min	12-13 min	18-19 min	17-19 min	14-15 min

N/A: Not applicable

Dissolution studies: The dissolution behaviour of pure Fenofibrate and solid dispersions with hydrophilic carriers prepared in different ratios was observed under the following parameters (**fig. 2, 3**);

Dissolution Parameters:

Medium : Water+0.75% Sodium lauryl sulfate
Apparatus : USP apparatus II (Paddles)
RPM : 75 RPM
Quantity : 900 ml
Temperature : 37 ± 0.5ºC
Time points : 15 min, 30 min, 45 min, 60 min.

Dissolution profile for pure fenofibrate and reference product: (Table 9)

TABLE 9*: IN-VITRO* DISSOLUTION PROFILE FOR PURE FENOFIBRATE AND REFERENCE PRODUCT

S. No.	Time (min)	Pure Fenofibrate (120 mg)	Reference product
1	15	7	59
2	30	18	79
3	45	22	90
4	60	24	99

Cumulative % Fenofibrate release for formulated batches and reference product: (Table 10, 11, 12)

TABLE 10: *IN-VITRO* DISSOLUTION PROFILE FOR TRIAL BATCHES AND INNOVATOR

Time	Innovator	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
15 min	59	N/A	N/A	N/A	N/A	1	68	65	69	57	58
30 min	79					2	88	85	83	80	81
45 min	90					4	98	95	91	89	93
60 min	99					6	100	98	99	98	100

N/A: Not applicable

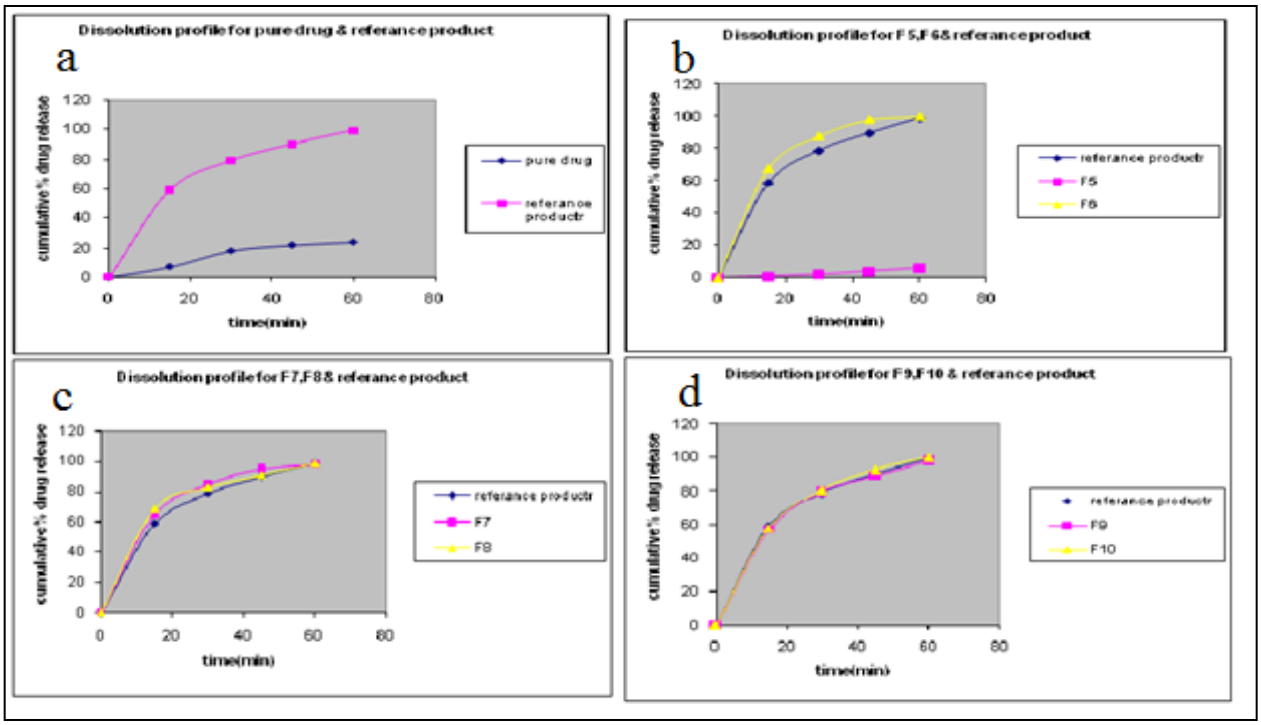

FIG. 2: A) *IN-VITRO* DISSOLUTION PROFILE FOR PURE FENOFIBRATE &INNOVATOR B) *IN-VITRO* DISSOLUTION PROFILE FOR F5,F6&REFERANCE PRODUCT C) *IN-VITRO* DISSOLUTION PROFILE FOR F7, F8 & REFERANCE PRODUCT D) *IN-VITRO* DISSOLUTION PROFILE FOR F9, F10 & REFERANCE PRODUCT

TABLE 11: DISSOLUTION PROFILE OF REPRODUCIBILITY BATCH (F10) COMPARED TO PURE FENOFIBRATE AND REFERANCE PRODUCT

S. No.	Time (min)	Pure Fenofibrate (120 mg)	Reference product	F10
1	15	7	59	58
2	30	18	79	81
3	45	22	90	93
4	60	24	99	100

TABLE 12: DISSOLUTION PROFILE OF REPRODUCIBILITY BATCH (F10) COMPARED TO PURE FENOFIBRATE AND PHYSICAL MIXTURE

S. No.	Time(min)	pure Fenofibrate (120 mg)	Physical mixture	F10
1	15	7	27	58
2	30	18	56	81
3	45	22	64	93
4	60	24	71	100

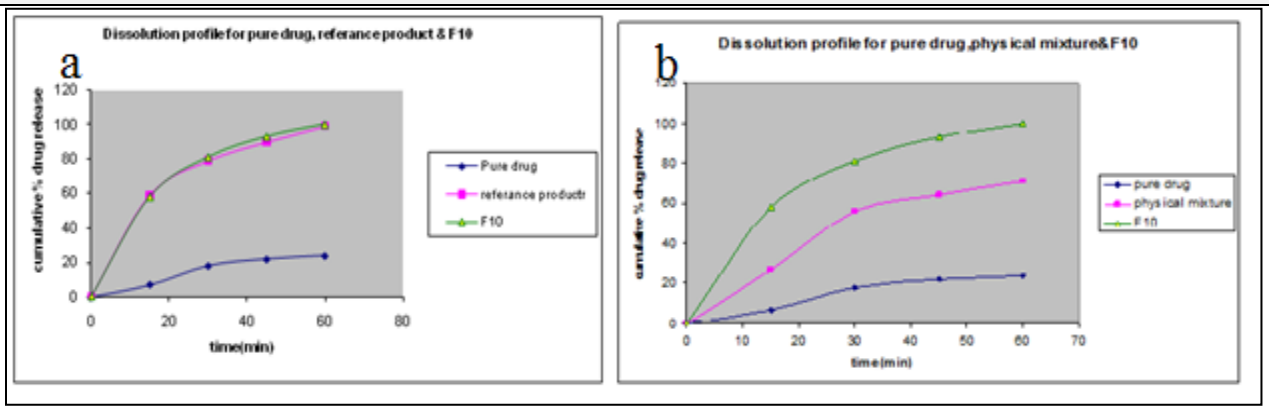

FIG. 3A): *IN-VITRO* DISSOLUTION PROFILE FOR PURE FENOFIBRATE, REFERANCE PRODUCT & F10; B): *IN-VITRO* DISSOLUTION PROFILE FOR PURE FENOFIBRATE, PHYSICAL MIXTURER & F10

Characterization of Solid dispersion: The solid-state properties of Fenofibrate in the solid dispersion were investigated using differential scanning calorimetry (DSC) since this would influence the *in vitro* and *in vivo* dissolution characteristics.

Differential Scanning Calorimetry: Thermal properties of Fenofibrate, polymer and solid dispersion were investigated using a METTLER differential scanning calorimeter thermal analysis controller with an intracooler-2 cooling. About 3 to 5 mg of product was placed in perforated aluminum sealed 50-µl pans, and the heat runs for each sample was set from 40°C to 250°C at 10°C/min, under an inert environment using nitrogen. The apparatus was calibrated using pure metals like indium with known melting points and heat of fusion (ΔH fusion) (**fig. 4, 5**).

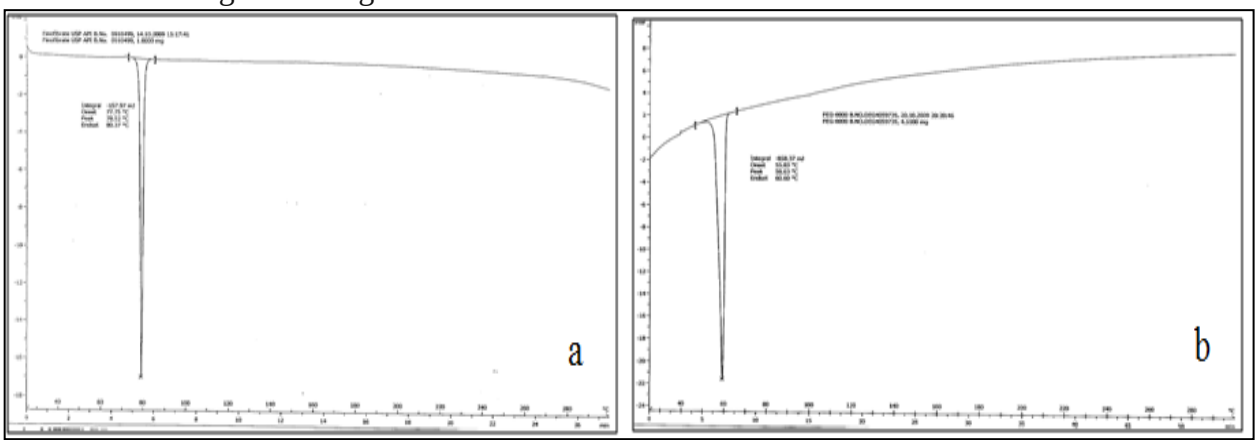

FIG. 4A): PURE FENOFIBRATE; B): PEG6000

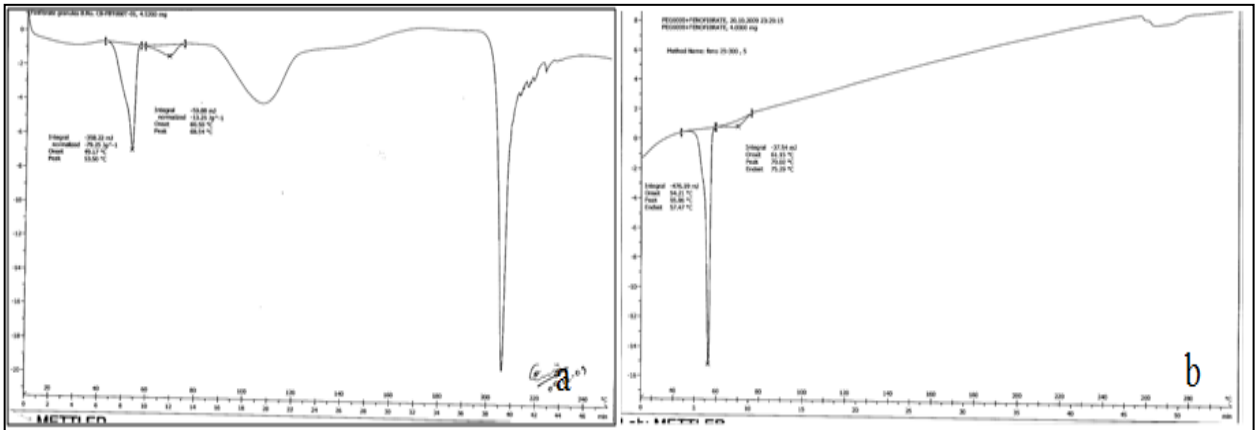

FIG. 5A): SOLID DISPERSION GRANULES (PRODUCT); B): PHYSICAL MIXTURE OF FENOFIBRATE & PEG 6000

The DSC for Solid dispersion of Fenofibrate shown shift in the melting point towards lower side compared to pure Fenofibrate. This shows conversion of maximum amount of Fenofibrate into amorphous form. The extra peak is due to placebo interference as shown in **fig. 4 and 6**.

Stability Studies: After 1month, 2month&3month period of stability studies Fenofibrate content and % Fenofibrate release studies are done. According to the data as shown in the **table 13**, Fenofibrate content and % release are within the limit.

TABLE 13: STABILITY DATA FOR F10

S. No.	% Fenofibrate release (60 min)	%Assay	Related substances (total impurity)
Initial	99	100.2	0.05
40/75, 1M	97	99.4	0.59
40/75, 2M	98	98.5	0.52
40/75, 3M	96	99.2	0.45

As the Fenofibrate content, % Fenofibrate release studies and related impurities are within the limit so the formulation passes the stability test. Optimization results of different formulations are tabulated in **tables 14 - 22.**

Effect of diluent (pre-gelatinized starch) concentration on the optimized batch:

TABLE 14: OPTIMIZATION OF DILUENT CONCENTRATION

Formulation	13.4%Diluent	8%Diluent	18%diluent
INTRAGRANULAR (mg/tablet)			
A.P.I	120	120	120
PEG6000	120	120	120
PEG400	24	24	24
DCM	310	310	310
IPA	200	200	200
Lactose monohydrate	366	366	366
EXTRAGRANULAR (mg/tablet)			
Pre-gelatinized starch	**135**	**80.60**	**181.34**
Crosscarmellose sodium	51	51	51
MCC	156	156	156
Aerosil	12	12	12
Magnesium stearate	18	18	18

Evaluation Parameters:

TABLE 15: EFFECT OF DILUENT ON TABLET CHARACTERISTICS

Formulation Code	Weight Variation	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration Time (sec)
13.4%	0.15	10.2-11.5	6.51-6.54	0.04	14-15min
8%	0.14	9.8-10.8	6.32-6.38	0.032	12-13min
18%	0.15	10.8-12.1	6.53-6.56	0.042	16-18min

Effect of diluent concentration on tablet dissolution profile:

TABLE 16*: IN VITRO* DISSOLUTION PROFILE

Time (min)	Referance product	13.4% Diluent	8% Diluent	18% diluent
		%Fenofibrate release		
0	0	0	0	0
15	59	60	71	62
30	79	82	97	88
45	90	95	102	94
60	99	100	103	96

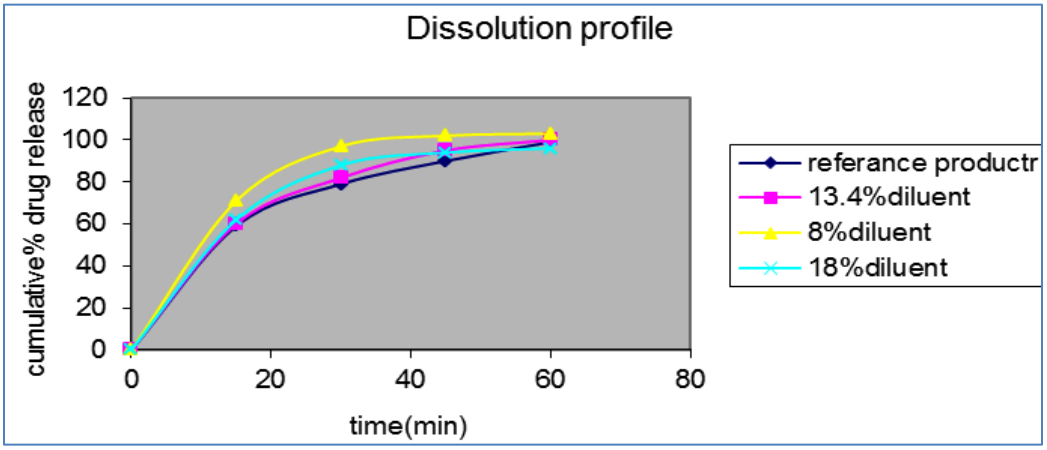

FIG. 6: DISSOLUTION PROFILE FOR EFFECT OF DILUENT

For diluent (pre-gelatinized starch), formulation were evaluated at different levels of 80.6mg and 181.34 mg, wherein significant differences were observed with respect to dissolution profile of the formulations. Hence pregelatinized starch at a level of 135 mg was required to obtain comparable product with the innovator product shown in **fig. 6**.

Effect of Disintegrant (Crosscarmellose sodium) concentration on the Optimized batch:

TABLE 17: OPTIMIZATION OF DISINTEGRANT CONCENTRATION

Formulation	5%Disintegranl	2.5%Disintegrant	7.5%disintegrant
INTRAGRANULAR (mg/tablet)			
A.P.I	120	120	120
PEG6000	120	120	120
PEG400	24	24	24
DCM	310	310	310
IPA	200	200	200
Lactose monohydrate	366	366	366
EXTRAGRANULAR (mg/tablet)			
Pre-gelatinized starch	135	135	135
Crosscarmellose sodium	**51**	**25.5**	**76.5**
MCC	156	156	156
Aerosil	12	12	12
Magnesium stearate	18	18	18

Evaluation Parameters:

TABLE 18: EFFECT OF DISINTEGRANT ON TABLET CHARACTERISTICS

Formulation Code	Weight Variation	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration Time (sec)
5%	0.15	10.2-11.5	6.51-6.54	0.04	14-15min
2.5%	0.12	10.1-10.8	6.48-6.49	0.042	16-18min
7.5%	0.14	10.3-10.9	6.50-6.52	0.039	9-11min

Effect of Disintegrant Concentration on Tablet Dissolution profile:

TABLE19: *IN-VITRO* DISSOLUTION PROFILE

Time (min)	Reference product	5% Disintegrant	2.5% Disintegrant	7.5% Disintegrant
		%Fenofibrate release		
0	0	0	0	0
15	59	60	51	81
30	79	82	70	96
45	90	95	88	100
60	99	100	98	100

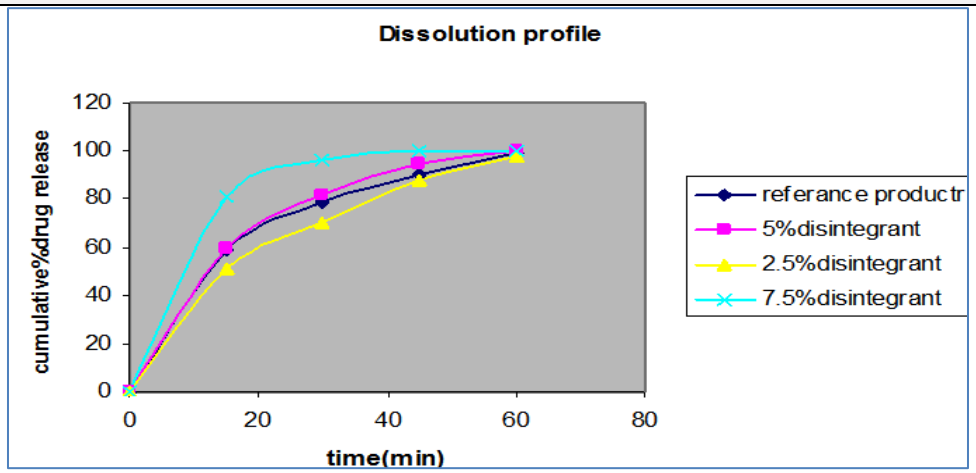

FIG. 7: DISSOLUTION PROFILE FOR EFFECT OF DISINTEGRANT

Disintegrant levels of 25.5mg and 76.5 mg were studied wherein significant difference was observed with respect to dissolution when disintegrant concentration was changed from 25.5 mg to 75.5 mg. A disintegrant level of 51 mg was required to obtain comparable product with the reference product shown in **fig. 7**.

Effect of Lubricant (Magnesium stearate) concentration on the Optimized batch:

TABLE 20: OPTIMIZATION OF LUBRICANT

Formulation	2%Lubricant	1% Lubricant t	3% Lubricant
INTRAGRANULAR (mg/tablet)			
A.P.I	120	120	120
PEG6000	120	120	120
PEG400	24	24	24
DCM	310	310	310
IPA	200	200	200
Lactose monohydrate	366	366	366
EXTRAGRANULAR (mg/tablet)			
Pre-gelatinized starch	135	135	135
Crosscarmellose sodium	51	51	51
MCC	156	156	156
Aerosil	12	12	12
Magnesium stearate	18	9	27

Evaluation Parameters:

TABLE 21: EFFECT OF LUBRICANT ON TABLET CHARACTERISTICS

Formulation Code	Weight Variation	Hardness (Kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration Time (sec)
5%	0.15	10.2-11.5	6.51-6.54	0.04	14-15min
2.5%	0.14	10-10.7	6.41-6.43	0.039	13-16min
7.5%	0.15	10.5-11.8	6.45-6.52	0.041	20-21min

Effect of Disintegrant concentration on Tablet Dissolution profile:

TABLE 22: *IN VITRO* DISSOLUTION PROFILE

Time (min)	Reference product	2%Lubricant	1% Lubricant t	3% Lubricant
	%Fenofibrate release			
0	0	0	0	0
15	59	60	66	59
30	79	82	80	75
45	90	95	96	90
60	99	100	99	96

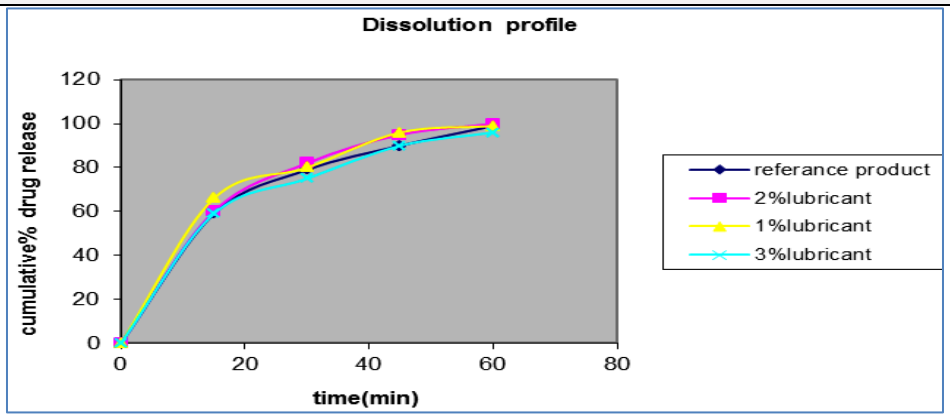

FIG. 8: DISSOLUTION PROFILE FOR EFFECT OF LUBRICANT

In case of lubricant, blend characteristics, physical attributes and dissolution profile of the formulation were evaluated at lubricant levels of 9 mg and 27 mg. A significant difference was observed with

respect to tablet characteristics and Fenofibrate release at lubricant concentration of 5 mg and a slower Fenofibrate release were observed at a concentration of 27 mg. The blend characteristics, physical attributes and dissolution profile of the formulation was acceptable at a lubricant concentration of 18 mg per tablet shown in **fig. 8**.

CONCLUSION: Immediate release oral dosage forms are most widely used Fenofibrate delivery systems available. These products are designed to disintegrate in the stomach followed by their dissolution in the fluids of the gastrointestinal tract. Dissolution of the Fenofibrate substance under physiological conditions is essential for its systemic absorption.

In this study, solid dispersion of poorly soluble Fenofibrate is prepared to enhance its solubility and Fenofibrate release profile.

Model Fenofibrate is of fibrate class used in the treatment of hypercholesterolemia and hyper-lipidemia. It reduces low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) levels, as well as increasing high-density lipoprotein (HDL) levels and reducing triglycerides level.

The Preformulation studies of API were carried out and Fenofibrate-Excipients compatibility studies were performed by physical observation. The physical observations have showed API-Excipients does not show any color changes and they were similar to that of initial samples, it showed that no physical changes were observed and found to be compatible.

The solid dispersion of model Fenofibrate was prepared by solvent evaporation method using Fluid-bed coater granulator.

F1 to F10 batches were prepared using hydrophilic polymer PEG 6000, surfactants PEG 400, cremophore EL, miglol and solvents IPA, DCM, inert carriers like lactose monohydrate, sugar spheres, celpheres. The Extragranular excipients used are micro-crystalline cellulose, pharmatose 200M, pregelatnized starch, Crosscarmellose sodium, aerosil 200, magnesium stearate

In preparation of batches F1 to F4 fluid- bed coater granulator process was not smooth due to presence of large amount of surfactants. For batches F5 to F8 process was smooth but Fenofibrate release profile is not matching with innovator. Batch F9 has similar dissolution profile as that of innovator so a reproducibility batch of F10 is done.

The solubility studies of solid dispersion in different media are done; there is increase in solubility compared to API.

The tablet parameters like weight variation, hardness, thickness, friability, disintegration time are passing all the specifications for batches F5 to F10.

Stability samples of F10 batch were analyzed for %Fenofibrate release and Fenofibrate content, they are within the limits.

Effect of diluent, disintegrant and lubricant concentrations was studied and the optimum concentration was selected based on Fenofibrate release profile.

Characterization of solid dispersion is done for batch F10 by DSC.

From the results. it could be concluded that solid dispersions can be prepared using fluid-bed coater granulator.

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