FORMULATION AND EVALUATION OF ORAL DISINTEGRATING TABLETS OF FENOFIBRATE BY WOWTAB TECHNOLOGY USING SOLID DISPERSION TECHNIQUE.

Dissertation work submitted to
The Tamilnadu Dr.M.G.R.Medical University, Chennai
In partial Fulfillment for the award of degree of

MASTER OF PHARMACY
IN
PHARMACEUTICS

Submitted by
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DEPARTMENT OF PHARMACEUTICS

R.V.S. COLLEGE OF PHARMACEUTICAL SCIENCES

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DECLARATION BY CANDIDATE

I hereby declare with immense pleasure and satisfaction that this dissertation work entitled "**Formulation and Evaluation of oral disintegrating tablets of Fenofibrate by WOWTAB Technology using Solid dispersion technique**" was carried out by me in the research and development center Matrix laboratories limited, Hyderabad under the guidance of **Dr.AKHILESH ASHOK DIXIT (Industrial guide)** senior General Manager and **Mr.BARISH (Institutional guide)** Assistant Professor Department of Pharmaceutics, R.V.S.College of Pharmaceutical Sciences, Sulur, Coimbatore .

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This is to certify that the research project work entitled "**Formulation And Evaluation Of Oral Disintegrating Tablets Of Fenofibrate By WOWTAB Technology Using Solid Dispersion Technique**" is a bonafide genuine work carried out by **Mr.VENKATESH PENDYALA (Reg.No.26106310)** in Partial fulfilment of the requirements for the award of degree in **Master of Pharmacy in Pharmaceutics** of **The Tamilnadu Dr.M.G.R.Medical University, Chennai**, in the research and development center of Matrix Laboratories Limited, Hyderabad under my guidance and supervision to my fullest satisfaction.

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VENKATESH.

LIST OF ABBREVATIONS USED

NCE	New Chemical Entities
WHO	World Health Organization
USP	United States Pharmacopoeia
RH	Relative Humidity
DSC	Differential Scanning Calorimeter
UV	Ultraviolet Spectroscopy
Mg	Milligram
Gm	Gram
M.wt	Molecular weight
µg/Ml	Microgram per milliliter
G.I.T	Gastro Intestinal Tract
SSF	Sodium stearyl fumarate
SSG	Sodium starch glycolate
CCS	Cros carmellose Sodium
HPMC	Hydroxy propyl methyl cellulose
HPC	Hydroxy propyl cellulose
BD	Bulk density
TD	Tapped density
HR	Hausner's ratio
C.I	Compressibility Index
ICH	International Conference on Harmonization
SCF	Super critical fluid
PVP	Polyvinyl pyrrolidone
PEG	Polyethylene glycol
w/w	Weight by weight
XRD	X-ray diffraction
SD	Solid dispersion
FTIR	Fourier transform infrared spectroscopy
Tg	Glass transition temperature

ODT	Oral disintegrating tablets
FDT	Fast dissolving tablets
SPH	Super porous hydrogel
P_b	Partial pressure
PSD	Particle size determination
API	Active pharmaceutical ingredient
PPXL	Polyplasdone XL
NMR	Nuclear magnetic resonance
LDL	Low density lipoproteins

HDL	High density lipoproteins

INDEX

ABSTRACT

Fenofibrate is a poorly water-soluble oral antihyperlipidemic agent belonging to fibrate class, with problems of variable bioavailability and bio-inequivalence related to its poor water-solubility. This work investigated the possibility of developing Fenofibrate tablets by **WOWTAB technology (with out water)** allowing fast, reproducible, and complete drug dissolution, by using solid dispersion of drug. Among various carriers used HPMC 3cps is forming a stable solid dispersion. Solubility studies were performed to investigate the drug-carrier interactions by both solvent evaporation and melt fusion method. DSC, X-ray powder diffraction, and FTIR studies were used to characterize the solid state of solid dispersions. The tablets were prepared by WOW technology by conventional granulation and tableting

methods employing low and high-moldability saccharides (Mannitol, sorbitol respectively) to have desired properties of rapid disintegration and hardness. The prepared tablets were evaluated thickness, uniformity of weight, content uniformity, hardness, friability, In vitro disintegration time. The tablets were subjected to moisture treatment to lower the DT. After moisture exposure tablets are evaluated for uniformity of weight, hardness, friability, In vitro disintegration time and In vitro drug release. The tablets apart from fulfilling all official and other specifications, the Fenofibrate dissolution profile from the newly developed tablets was clearly better than those from various conventional tablets of the same drug dosage. The stability studies conducted as per ICH guidelines at 40° and 75% RH showed insignificant loss in drug content and on physical evaluations at the end of six months.

Key terms: Solid dispersion, WOWTAB technology, Saccharides, Moisture treatment

I. INTRODUCTION

Solid oral drug delivery is the simplest and easiest way of administering drugs. These dosage forms have many advantages over other types of oral dosage forms. Therefore, most of the New Chemical Entities (NCE) under development are intended to be used as a solid dosage forms that originate an effective and reproducible in vivo plasma concentration after oral administration.

The aqueous solubility of a drug is one of the key physical properties that affect both its ADME profile and 'screen ability' in High Throughput Screening (HTS). Solubility is the characteristic physical property referring to 'the ability of a given substance, the solute, to dissolve in a solvent'. Enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Solubility and dissolution are the rate determining steps in drug absorption.

Table 1: Solubility Terms (According to USP)

Definition	Parts of solvent required for one part of solute
Very Soluble	<1
Freely Soluble	1-10
Soluble	10-30
Sparingly Soluble	30-100
Slightly Soluble	100-1000
Very Slightly Soluble	1000-10,000
Insoluble	> 10,000

Biopharmaceutical Classification System categorized poorly soluble and highly permeable drugs under class II. Nearly 40 % of the drug molecules that have been discovered are lipophilic in nature.

Table 2: Biopharmaceutical Classification System (According to BCS classification by FDA)

Class	Description
Class I	Highly soluble, highly permeable
Class II	Poorly soluble, highly permeable
Class III	Highly soluble, Poorly permeable
Class IV	Poorly soluble, Poorly permeable

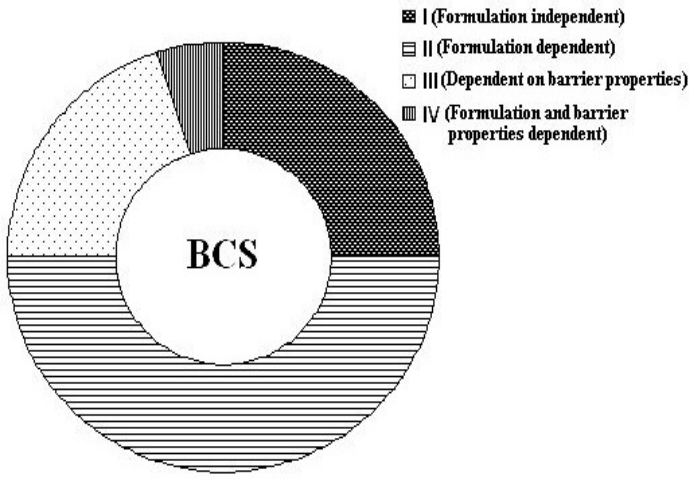


Figure 1: Graphical representation of Biopharmaceutical Classification System

1.1 Factors Affecting Solubility

Several factors affect solubility of a drug. The following are the factors that affect solubility (K Patidar et al., 2011).

1. Particle Size
2. Temperature
3. Pressure
4. Nature of the solute and solvent
5. Molecular size
6. Polarity
7. Polymorphs

1.2 Approaches for increasing solubility (Bell LN et al.,1995).

A) Formulation approach

a) Reduction in particle size by

i) Micronization technique

ii) Nanosuspension formulation.

b) Modification of the crystal habits

c) Complexation of drug as

i) Inclusion complex

ii) Ion exchange complex

d) Solubilization and surfactants

i) Micronization

ii) Micelles formation

iii) Formulation of self-emulsifying drug delivery systems

e) Formation of solid dispersions with water soluble carriers.

B) Chemical modification

a) Salt formation

b) Prodrug formation

c) Polar group incorporation

1.3 INTRODUCTION TO SOLID DISPERSIONS

Solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drugs. By reducing drug particle size to the absolute minimum, and hence improving drug wettability, solubility increases hence bioavailability may be significantly improved. They are usually presented as amorphous products, mainly obtained by two major different methods, melting and solvent evaporation(Abu T.M. Serajuddin., 1999).

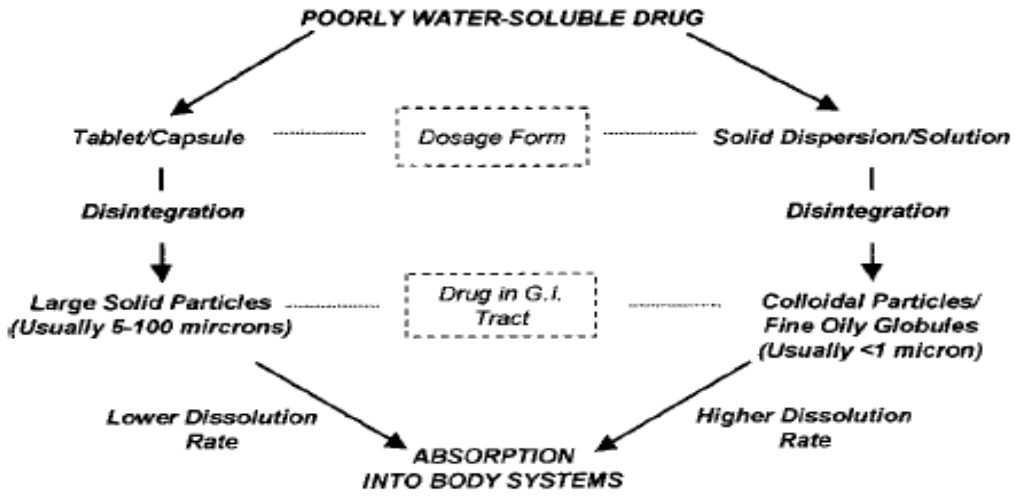


Figure 2: A schematic representation of the bioavailability enhancement of a poorly soluble drug by solid dispersion compared with conventional tablet or capsule.

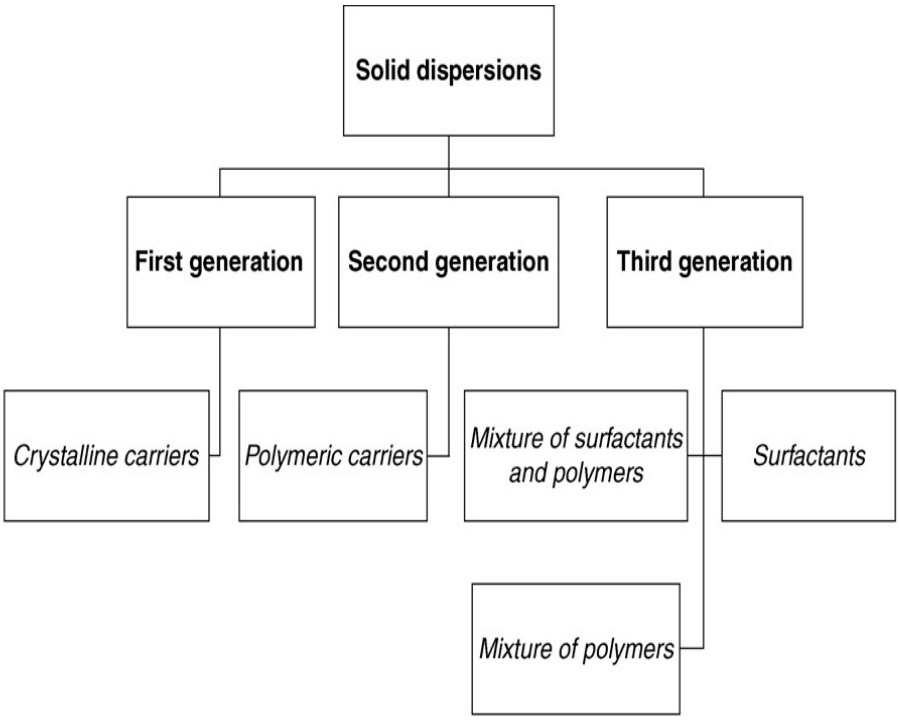


Figure 3: The classification of solid dispersions (Teófilo Vasconcelos et al., 2007).

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. Alternatively, solid dispersions can be used to increase the dissolution rate of poorly soluble drugs, and they have proven to increase the amount of dissolved drug at the absorption site sometimes to supersaturated concentrations and consequently improve the bioavailability. 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 3: Types of solid dispersions (D.J. van Drooge, 2006).[34]

Solid Dispersion Type		Matrix	Drug	No. of Phases
I	Eutectics	Crystalline	Crystalline particles	2
II	Amorphous Precipitations in crystalline matrix	Crystalline	Amorphous clusters	2
III	**Solid solutions**			
	Continuous solid solutions	Crystalline	Molecularly dispersed	1
	Discontinuous solid solutions	Crystalline	Molecularly dispersed	2
	Substitutional solid solutions	Crystalline	Molecularly dispersed	1 or 2
	Interstitial solid solutions	Crystalline	Molecularly dispersed	2
IV	Glass suspension	Amorphous	Crystalline particles	2
V	Glass suspension	Amorphous	Amorphous clusters	2
VI	Glass solution	Amorphous	Molecularly dispersed	1

1.3.1 Advantages of solid dispersion (D.J. van Drooge, 2006)[34]

1. Particles with reduced particle size

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers, a high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability.

2. Particles with improved wettability

A strong contribution to the enhancement of drug solubility is related to the improvement of drug wettability of solid dispersions.

3. Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.

4. Drugs in amorphous state

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form.

For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.

Table 4: Materials used as carriers for Solid Dispersions (Ingel U.S et al., 2011).[39]

Materials	Examples
Sugars	Dextrose, Sucrose, Galactose, Sorbitol, Maltose, Mannitol, Xylitol, Lactose.
Acids	Citric acid, succinic acid
Polymeric materials	Povidone (PVP), (Poly ethylene glycol) (PEG), Hydroxy propyl methyl cellulose, methyl cellulose, Hydroxy ethyl cellulose, cyclodextrins, Hydroxy propyl cellulose, Pectin, Gal.
Insoluble or enteric polymers	Hydroxy propyl -methyl cellulose phthalate, Eudragit L-100, Eudragit S- 100, Eudragit RL, Eudragit RS.
Surfactants	Polyoxyethylene stearate, Renex, Poloxamer 188, Texafor AIP, Deoxycholic acid, Tweens, Spans.
Miscellaneous	Pentaerythritol, Pentaerythrityl tetra acetate, urea, urethane, Hydroxyalkylxanthins.

1.3.2 METHODS OF PREPARATION OF SOLID DISPERSIONS

Various preparation methods for solid dispersions have been reported in literature.

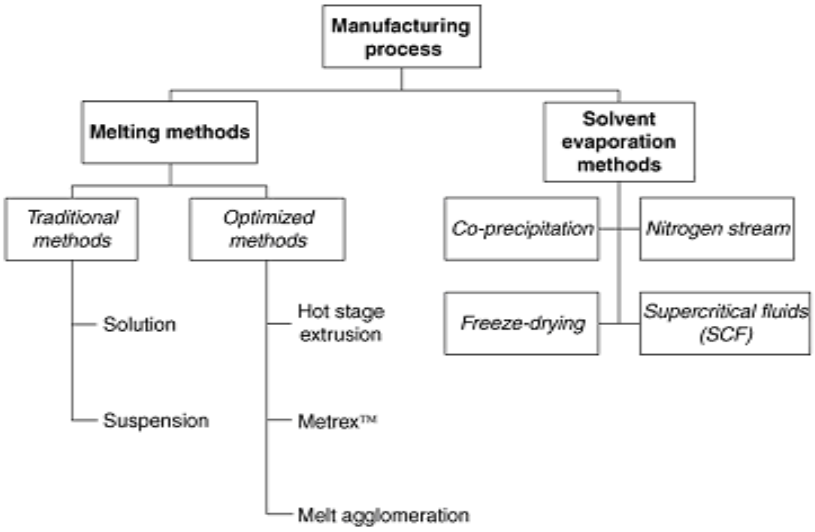


Figure 4: Manufacturing processes used to produce solid dispersions (Gaurav Tiwari et al., 2009).[24]

Solvent evaporation

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents.

Melting/fusion method

The melting or fusion method involves the preparation of physical mixture of a drug and a water soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures.

Advantages of melting methods

1) Economic
2) Solvent less process

Disadvantages of melting methods

1) This method is not suitable for the drug or carrier unstable at fusion temperature or evaporates at higher temperature.
2) Solidification temperature may affect crystallization rate and hardness of the dispersion.
3) Irregular crystallization owing to the presence of a miscibility gap on the phase diagram for a given drug-carrier system.

In 1961, Sekiguchi and Obi formed eutectic mixtures of drugs with water-soluble carriers by melting their physical mixtures. This was a significant advance in the development of solid dispersion systems.

Solvent-melting method (melt evaporation)

This method involves dissolving the drug in a suitable organic solvent and then incorporating the solution directly into the molten carrier, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. This method is particularly useful for drugs having high melting points or which are thermolabile. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg.

Melt Agglomeration Process

This technique has been used to prepare Solid Dispersion wherein the binder acts as a carrier. In addition, SD(s) are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt- in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer. A rotary processor has been shown to be alternative equipment for melt agglomeration because of easier control of the temperature and because higher binder content can be incorporated in the agglomerates. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of SD(s) by melt agglomeration. It has been investigated that the melt in procedure gives a higher dissolution rates than the spray-on

procedure with PEG 3000, poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. In addition the melt in procedure also results in homogenous distribution of drug in agglomerate.

Lyophilization Technique

Freeze-drying involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophilization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.

Melt extrusion

Melt extrusion is a new method for producing solid dispersions. Special equipment is needed to develop the dosage form from solid dispersions, which limits the use of the extrusion method. Forster et al. report the use of melt extrusion to prepare glass solutions of poorly water-soluble drugs with hydrophilic excipients. It is claimed that the method is an improvement to existing formulation methods such as spray-drying and co-melting because it uses smaller quantities of drug, reduces particle size and speeds up the formulation process.

Electrospinning Method

The electrospinning technology used in the polymer industry combines solid solution/ dispersion technology with nanotechnology. In this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are formed. As the solvent evaporates, the formed fibers can be collected on a screen to give a nonwoven fabric, or they can be collected on a spinning mandrel. The fiber diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest and the cheapest this technique can be utilized for the preparation of solid dispersions in future.

Dropping solution Method:

The dropping method, developed by Ulrich *et al.* (1997) to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. This technique may overcome some of the difficulties inherent in the other methods.

For laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Because viscosity is highly temperature-dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape. The use of carriers that solidify at room temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process, but also gives a higher dissolution rate. It does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation. The method also avoids the pulverization, sifting and compressibility difficulties encountered with the other melt methods. Disadvantages of the dropping method are that only thermostable drugs can be used and the physical instability of solid dispersions is a further challenge.

Alternative strategies

Spraying on sugar beads using a fluidized bed coating system

The approach involves a fluidized bed coating system, wherein a drug-carrier solution is sprayed onto the granular surface of excipients or sugar spheres to produce either granules ready for table ting or drug-coated pellets for encapsulation in one step. The method has been applied for both controlled- and immediate-release solid dispersions.

Hot-melt extrusion

Melt extrusion was used as a manufacturing tool in the pharmaceutical industry as early as 1971. [20] Since the turn of the century, many studies have been conducted on this

process for the preparation of solid dispersion. It has been reported that melt extrusion of miscible components results in amorphous solid solution formation, whereas extrusion of an immiscible component leads to amorphous drug dispersed in crystalline excipient. [21] The process has been useful in the preparation of solid dispersions in a single step. Hot-melt extrusion method is used in the preparation of various dosage forms in the pharmaceutical industry such as preparation of sustained-release pellets.

Direct capsule filling

The filling of semisolid materials into hard gelatin capsules as melts, which solidify at room temperature, was first done in 1978. Laboratory-scale semiautomatic equipment and large-scale manufacturing equipment for direct capsule filling are commercially available. Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique. However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug. A surfactant must be mixed with the carrier to avoid formation of a drug-rich surface layer (*e.g.* polysorbate 80 with PEG, phosphatidylcholine with PEG). The temperature of the molten solution should not exceed ~70^0C because it might compromise the hard-gelatin capsule shell.

Surface-active carriers

A surface-active carrier may be preferable in almost all cases for the solid dispersion of poorly water-soluble drugs. The surface-active and self-emulsifying carriers for solid dispersion of poorly water-soluble drugs have been of great interest in recent years.

Two of the important surface-active carriers are Gelucire 44/14 and Vitamin E R-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). Gelucire 44/14 (Gattefosse Corp, Gennevilliers, France) has commonly been used in solid dispersion for the bioavailability enhancement of drugs.

A commonly used surfactant, Polysorbate 80, when mixed with solid PEG, has also been reported to be an alternative surface-active carrier. Polysorbate 80 is liquid at room temperature; it forms a solid matrix when it is mixed with a PEG because it incorporates within the amorphous regions of PEG solid structure.

Initial formulation development studies can be conducted by filling hot solutions or dispersions into hard-gelatin capsule shells manually by using pipettes or by using laboratory-scale semiautomatic equipment.

Supercritical fluid technology(SCF)

It has been known for more than a century that supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide, the most widely used supercritical fluid. SCF technology offers tremendous potential, as it is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research.

In the pharmaceutical field, the SCF technology was industrially applied in the early 1980s; the applications included the purification of surfactants and pharmaceuticals, fractionation of polymeric materials and chemical reactions and polymerizations. In the same period, interest in using SCFs for precipitation and crystallization processes was developing for pharmaceutical materials. A SCF exists as a single phase above its critical temperature (Tc) and pressure (Pc). SCFs have properties useful to product processing because they are intermediate between those of pure liquid and gas (i.e., liquid-like density, gas-like compressibility and viscosity and higher diffusivity than liquids). Moreover, the density, transport properties (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and polarity) vary considerably with small changes in operating temperature, pressure, or both around the critical points. Hence, it is possible to fine-tune a unique combination of properties necessary for a desired application (Patidar Kalpana et al.,2010).

The limitations of this technology have been a drawback for the commercialization of solid dispersions.[35]

The limitations include:

1. Laborious and expensive methods of preparation,
2. Reproducibility of physicochemical characteristics,
3. Difficulty in incorporating into formulation of dosage forms,
4. Scale-up of manufacturing process, and
5. Stability of the drug and vehicle.

1.3.3 TECHNIQUES TO EXPLORE MOLECULAR INTERACTIONS AND BEHAVIOR (Gaurav Tiwari et al.,2009).[(24)]

Drug –carrier miscibility

- Hot stage microscopy

- DSC (Conventional modulated)
- pXRD (Conventional and variable temp)
- NMR 1H Spin lattice relaxation time

Drug carrier interactions

- FT-IR spectroscopy
- Raman spectroscopy
- Solid state NMR

Physical Structure

- Scanning electron microscopy
- Surface area analysis

Surface properties

- Dynamic vapor sorption
- Inverse gas chromatography
- Atomic force microscopy
- Raman microscopy

Amorphous content

- Polarized light optical microscopy
- Hot stage microscopy
- Humidity stage microscopy
- DSC (MTDSC)
- ITC
- pXRD

Stability

- Humidity studies
- Isothermal calorimetry
- DSC (glass transition temperature(Tg), Temperature recrystallization)
- Dynamic vapor sorption
- Saturated solubility studies

Dissolution enhancement

- Dissolution
- Intrinsic dissolution
- Dynamic solubility
- Dissolution in bio-relevant media

1.4 DISEASE PROFILE

Hypercholesterolemia

Hypercholesterolemia (literally: high blood cholesterol) is the presence of high levels of cholesterol in the blood. It is not a disease but a metabolic derangement that can be secondary to many diseases and can contribute to many forms of disease, most notably cardiovascular disease. It is closely related to the terms "hyperlipidemia" (elevated levels of lipids) and "hyperlipoproteinemia" (elevated levels of lipoproteins).

Causes:

Diet -Cholesterol levels can increase by a high intake of saturated fat, excess calories and dietary cholesterol. Also, HDL levels can decrease and LDL level increase if person is overweight.

Heredity - The way individual's body makes and handles cholesterol can be a matter of genes, as well as diet and lifestyle.

Medical conditions - Elevated cholesterol can be caused by conditions such as liver disease, diabetes, kidney disease or thyroid disease.

Age and gender - Men and women at around the age of 20 starts to raise their cholesterol level. Compared with men of the same age, pre-menopausal women usually have lower levels of cholesterol. After menopause, women risks for heart disease increase since their LDL cholesterol levels typically go up.

Physical activity - Lack of exercise can cause a raise in the LDL levels and a lowering in the HDL levels. Increased physical activity will cause the opposite.

Alcohol use: Moderate alcohol intake increases HDL cholesterol but does not lower LDL cholesterol. Doctors don't know for certain whether alcohol also reduces the risk of heart disease. Drinking too much alcohol can damage the liver and heart muscle, lead to high blood pressure, and raise triglyceride levels. Because of the risks, alcoholic beverages should not be used as a way to prevent heart disease.

Mental stress Stress raises blood cholesterol levels over the long term. One way that stress may do this is by affecting your habits. For example, when some people are under stress, they console themselves by eating fatty foods. The saturated fat and cholesterol in these foods contribute to higher levels of blood cholesterol.

Signs and symptoms:

Symptoms that may occur include:

- Fatty, cholesterol-rich skin deposits (xanthomas)
- Cholesterol deposits in the eyelids (xanthelasmas)
- Chest pain (angina) associated with coronary artery disease
- Obesity

Persons with either one or two copies of the defective gene can develop fatty skin deposits over their elbows, knees, buttocks, tendons, and around the cornea of the eye.

1.5 Dysphagia and Fast Disintegrating Tablets (FDTs)

Dysphagia, or difficulty in swallowing, is common among all age groups. According to a study by Sastry et al., dysphagia is common in about 35% of the general population, as well as an additional 30–40% of elderly institutionalized patients and 18–22% of all persons in long-term care facilities. Common complaints about the difficulty in swallowing tablets in the order of frequency of complaints are size, surface, form, and taste of tablets. Geriatric and pediatric patients and traveling patients who may not have ready access to water are most in need of easy swallowing dosage forms. Another study shows that an estimated 50% of the population suffers from this problem. These studies show an urgent need for a new dosage form that can improve patient compliance. Solid dosage forms that can be dissolved or suspended with water in the mouth for easy swallowing are highly desirable for the pediatric and geriatric population, as well as other patients who prefer the convenience of readily administered dosage forms. Although chewable tablets have been on the market for some time, they are not the same as the new **oral disintegrating tablets (ODTs).**

Patients for whom chewing is difficult or painful can use these new tablets easily. ODTs can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth**.** Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms and most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (>80%)**.** During the last decade, **fast disintegrating tablet (FDT)** technologies that make tablets disintegrate in the mouth without chewing and additional water intake have drawn a great deal of attention.

The FDT is also known as *fast melting, fast dispersing, rapid dissolve, rapid melt,* and/or *quick disintegrating tablet.* All FDTs approved by the Food and Drug Administration (FDA) are classified as orally disintegrating tablets. Recently, the European Pharmacopeia adopted the term *orodispersible tablet* for a tablet that disperses or disintegrates in less than 3 minutes in the mouth before swallowing. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients. The disintegration time for good FDTs varies from several seconds to about a minute.

1.5.1 Advantages of FDTs

FDTs have all the advantages of solid dosage forms, such as good stability, accurate dosing, easy manufacturing, small packaging size, and easy handling by patients. FDTs also have the advantages of liquid formulations, such as easy administration and no risk of suffocation resulting from physical obstruction by a dosage form.

The primary patients for FDTs are pediatric, geriatric, and bedridden or developmentally disabled patients; patients with persistent nausea; and patients who have little or no access to water. Application of FDTs can of course be extended to more general patients of daily medication regimens. From the pharmaceutical industry's point of view, FDTs can provide new dosage forms as a life cycle management tool for drugs near the end of their patent life.

Because the tablets disintegrate inside the mouth, drugs may be absorbed in the buccal, pharyngeal, and gastric regions. Thus, rapid drug therapy intervention and increased bioavailability of drugs are possible. Because the pre-gastric drug absorption avoids the first-pass metabolism, the drug dose can be reduced if a significant amount of the drug is lost through the hepatic metabolism.

1.5.2. DESIRED CHARACTERISTICS AND DEVELOPMENT CHALLENGES OF FAST DISSOLVING TABLETS (FDT):

Because administration of FDTs is different from administration of conventional tablets, the FDTs should maintain several unique properties, as listed below.

A. Fast Disintegration

FDTs should disintegrate in the mouth without additional water or with a very small amount (e.g., 1–2 ml) of water. The disintegration fluid is provided by the saliva of the patient. The disintegrated tablet should become a soft paste or liquid suspension, which can provide good mouth feel and smooth swallowing. The "fast disintegration" usually means disintegration of tablets in less than 1 minute, but it is preferred to have disintegration as soon as possible.

B. Taste of Active Ingredients

Because FDTs dissolve or disintegrate in the patient's mouth, the drug will be partially dissolved in close proximity to the taste buds. After swallowing, there should be minimal or no residue in the mouth. A pleasant taste inside the mouth becomes critical for patient acceptance. Unless the drug is tasteless or does not have an undesirable taste, taste-masking techniques should be used.

An ideal taste-masking technology should provide drugs without grittiness and with good mouth feel. The amount of taste-masking materials used in the dosage forms should be kept low **"AS LOW AS POSSIBLE"** to avoid excessive increase in tablet size. The taste-masking technology should also be compatible with FDT formulations. For example, if drug particles are coated to minimize unpleasant taste, the coating should not be broken during compression or dissolved during wet granulation. Taste masking of bitter tasting drugs is critical to the success of the FDT formulations.

C. Drug Properties

For the ideal FDT technology, the drug properties should not significantly affect the tablet property. Many drug properties could potentially affect the performance of FDTs. For example, the solubility, crystal morphology, particle size, hygroscopicity, compressibility, and bulk density of a drug can significantly affect the final tablet's characteristics, such as tablet strength and disintegration. The FDT technology should be versatile enough to accommodate unique properties of each drug.

Several factors must be considered when selecting drug candidates for delivery as ODT dosage forms. In general, an ODT is formulated as a bioequivalent line extension of an existing oral dosage form. Under this circumstance, it is assumed that the absorption of a drug molecule from the ODT occurs in the postgastric GIT segments, similar to the conventional oral dosage form. But this scenario may not always be the case. An ODT may have varying degrees of pre gastric absorption and thus, the pharmacokinetic profiles will vary. Therefore, the ODT will not be bioequivalent to the conventional oral dosage form. For example, ODT formulations of selegiline, apomorphine, and buspirone have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form. It is possible that these differences may, in part, be attributed to the drug molecule, formulation, or a combination of both. If significantly higher plasma

levels have been observed, pregastric absorption leading to the avoidance of first-pass metabolism may play an important role. This situation may have implications for drug safety and efficacy, which may need to be addressed and assessed in a marketing application for an ODT**.**

For example, safety profiles may be improved for drugs that produce a significant amount of toxic metabolites mediated by first pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and segments of the pregastric GIT. Drugs having ability to diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferable > 2); and those able to permeate oral mucosal tissue are considered ideal for ODT formulations. Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs. Similarly, patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations.

Drugs with a short half-life and frequent dosing, drugs which are very bitter or otherwise unacceptable taste because taste masking cannot be achieved or those which require controlled or sustained release are unsuitable candidates of rapidly dissolving oral dosage forms. Researchers have formulated ODT for various categories of drugs used for therapy in which rapid peak plasma concentration is required to achieve the desired pharmacological response. These include neuroleptics, cardiovascular agents, analgesics, antiallergic, anti-epileptics, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction**.**

D. Tablet Strength and Porosity

Because FDTs are designed to have a quick dissolution/disintegration time, the tablet porosity is usually maximized to ensure fast water absorption into the tablets. The key properties of the tablets are fast absorption or wetting of water into the tablets and disintegration of associated particles into individual components for fast dissolution. This requires that excipients should have high wettability, and the tablet structure should also have a highly porous network. Because the strength of a tablet is related to compression pressure, and porosity is inversely related to compression pressure, it is important to find the porosity that allows fast water absorption while maintaining high mechanical strength. In addition, low

compression pressure causes fast dissolving dosage forms to be soft, friable, and unsuitable for packaging in conventional blisters or bottles. A strategy to increase tablet mechanical strength without sacrificing tablet porosity or requiring a special packaging to handle fragile tablets should be provided.

E. Moisture Sensitivity

FDTs should have low sensitivity to humidity. This problem can be especially challenging because many highly water-soluble excipients are used in formulation to enhance fast dissolving properties as well as to create good mouth feel. Those highly water-soluble excipients are susceptible to moisture; some will even deliquesce at high humidity. A good package design or other strategy should be created to protect FDTs from various environmental conditions.

F. Palatability

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance.

G. Amount of drug

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers

H. Aqueous solubility

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that

may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.

I. Size of tablet

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

Various patents involved in ODT are mentioned in Table no 5

Advantages and disadvantages of ODT's are mentioned in table no 6

1.5.3 Approaches to ODT Development

The fast disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to develop rapidly dissolving oral dosage forms include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water soluble excipients in the formulation**.** As is often the case, a technology that is originally developed to address a particular administration need can quickly become adopted as part of a pharmaceutical company's product life cycle management strategy, which is precisely what has happened with ODT technologies. Several patented technologies with their basis of formulation are listed in Table 5. The technologies that have been used by various researchers to prepare orally disintegrating dosage forms include:

1. Freeze- Drying or Lyophilization,
2. Molding,
3. Direct Compression,
4. Disintegrant addition,
5. Sublimation,
6. Spray Drying,
7. Mass Extrusion,
8. Cotton-candy process,
9. NanoCrystalTM Technology,
10. Oral films/wafers.

Marketed products of the various ODT technologies are listed in table 7

Some ODT patents

Technology	Basis	Patent owner
Zydis	Lyophilization	R.P.Scherer Inc.
Quicksolv	Lyophilization	Janseen Pharmaceutica
Lyoc	Lyophilization	Farmlyoc
Flashtab	Multiparticulate Compressed Tablets	Ethypharm
Orasolv, Durasolv	Compressed Tablets	Cima Labs Inc.
RapiTab	Compressed Tablets	Schwarz Pharma
WOWTAB	Compressed Molded Tablets	Yamanouchi Pharma Technologies, Inc.
Fast melt	Molding	Élan Corp.
Ziplets	Molding	Eurand
FlashDose	Cotton-candy process	Fuisz Technology Ltd.

TABLE NO.5: ODT PATENTS

TABLE NO. 6 ADVANTAGES AND DISADVANTAGES OF ODT TECHNOLOGIES

Technique	Novelty	Advantage(s)	Disadvantage(s)
Zydis	First to market, Freeze dried	Quick dissolution, Self-preserving, increased bioavailability	Expensive process, poor stability at higher temperatures and humidities
Orasolv	Unique taste-masking, lightly compressed	Taste-masking is two-fold, quick dissolution	Low mechanical strength
Durasolv	Compressed dosage form, Proprietary taste masking.	Higher mechanical strength than Orasolv, good rigidity	Inappropriate with larger doses.
Flash Dose	Unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy.	High surface area for dissolution.	High temperature required to melt the matrix can limit he use of heat-sensitive drugs, sensitive to moisture and humidity.
Flashtab	Compressed dosage form containing drug as microcrystals.	Only conventional tableting technology is required.	--
Wowtab	Combination of low-mouldability and high-mouldabiity saccharides. SMOOTHMELT action gives superior mouth feel.	Adequate dissolution rate and hardness.	No significant change in bioavailability.
Oraquick	Uses patented taste-masking technology.	Faster and efficient production, appropriate for heat-sensitive drugs	--

Ziplet	Incorporation of water-insoluble inorganic excipients for excellent physical performance	Good mechanical strength, handling problems during manufacturing are avoided, satisfactory properties can be obtained at high dose (450 mg) and high weight (850 mg)	As soluble component dissolves, rate of water diffusion in to tablet is decreased because of formation of viscous concentrated solution.

TABLE NO. 7: SOME OF THE MARKETED ODT FORMULATIONS

Brand name	Active ingredient	Application	Company	Technology
Claritin® RediTabs®	Loratadine	Antihistamine	Schering Corporation	Zydis®
Feldene Melt®	Piroxicam	NSAID	Pfizer	
Maxalt®-MLT®	Rizatritpan benzoate	Migrane	Merck	
Pepcid® ODT	Famotidine	Anti-ulcer	Merck	
Zyprexa®	Olanzapine	Psychotic disorders	Eli Lilly	
Zofran® ODT®	Ondansetron	Anti-emetic	Glaxo Smith Kline	
Risperdal® M-Tab™	Risperidone	Schizophrenia	Janssen	
Zubrin™(pet drug)	Tepoxalin	Canine NSAID	Schering Corporation	
Zelapar™	Selegiline	Parkinson's disease	Elan / Amarin Corporation	
Klonopin® Wafers	Clonazepam	Sedation	Roche	
Children's Dimetapp® ND	Loratadine	Allergy	Wyeth Consumer Healthcare	
Imodium Instant Melts	Loperamide HCl	Anti-diarrheal	Jannsen	
Propulsid® Quicksolv®	Cisapride monohydrate	Gastrointestinal prokinetic agent	Janssen	Quicksolv®
Tempra Quicklets Tempra FirsTabs	Acetaminophen	Analgesic	Bristol-Myers Squibb	OraSolv®
Remeron® SolTab®	Mirtazapine	Anti-depression	Organon Inc.	
Triaminic® Softchews®	Various combinations	Pediatric cold, cough and allergy	Novartis Consumer Health	

Zomig-ZMT® and Rapimelt®	Zolmitriptan	Anti-migraine	AstraZeneca	DuraSolv®
Alavert®	Loratadine	Allergy	Wyeth Consumer Healthcare	
NuLev®	Hyoscyamine sulfate	Anti-ulcer	Schwarz Pharma	
Kemstro™	Baclofen	Anti-spastic analgesic	Schwarz Pharma	
Benadryl® Fastmelt®	Diphenhydramine citrate	Allergy, sinus pressure relief	Pfizer	WOWTAB®
Nasea OD	Ramosetoron HCl	Anti-emetic	Yamanouchi	
Gaster D	Famotidine	Anti-ulcer	Yamanouchi	
Excedrin® QuickTabs	Acetaminophen	Pain reliever	Bristol-Myers Squibb	QuickTabs™
Ralivia FlashDose®	Tramadol HCl	Analgesics	Biovail	FlashDose®
Zolpidem ODT	Zolpidem tartrate	Sleep disorders	Biovail	
Fluoxetine ODT	Fluoxetine	Anti-depression	Biovail	
Nurofen® Flashtab®	Ibuprofen	NSAID	Boots Healthcare	Flashtab®
Hyoscyamine Sulfate ODT	Hyoscyamine sulfate	Anti-ulcer	ETHEX Corporation	OraQuick
Cibalginadue FAST	Ibuprofen	NSAID	Novartis Consumer Health	Ziplets™

1.6 WOWTAB® Technology

WOWTAB technology employs a combination of low- and high-moldability saccharides to produce fast-dissolving tablets using conventional granulation and tableting techniques. According to the patent, saccharides were divided into two groups:

- Those with **high moldability** and
- Those with **low moldability**.

Low moldability saccharides produce tablets with hardness between 0 and 2 kg, when 150 mg of such a saccharide is compressed under pressure of 10–50 kg/cm using a die 8 mm in diameter.

The typical low-moldability saccharides include lactose, mannitol, glucose, sucrose, and xylitol.

High-moldability saccharides produce tablets with hardness above 2 kg when prepared under the identical conditions. The typical high- moldability saccharides are maltose, maltitol, sorbitol, and oligosaccharides.

When tablets are made by compressing a saccharide having low moldability or high moldability alone, the desired properties of adequate hardness and quick disintegration in the mouth cannot be achieved simultaneously. Moreover, if saccharides having low moldability and high moldability are mixed (physical mixture) before tableting, quick disintegration and dissolution in the mouth cannot be obtained. As clearly indicated in the patents, there is no single saccharide that can make tablets having both high strength and fast disintegration properties. For this reason, a saccharide having low moldability was granulated with a saccharide having high moldability as a binder. The low-moldability saccharides were used as the main component. Tablets made by compression of these granules were further treated under moisture condition as described in Figure 5. The tablets show an adequate hardness and fast disintegration and dissolution when put in the mouth.

Intrabuccally dissolving compressed moldings comprising of saccharide with low moldability having been granulated with saccharide having high moldability. These moldings show quick disintegration and dissolution in the buccal cavity and have an adequate hardness and suitable for both bottle packing and blister packing.

The term "intra buccally dissolving compressed moldings" means they have a practically sufficient disintegration and dissolution by saliva by merely keeping in the mouth with out holding water in the buccal cavity and which have adequate hardness.

The term "practically sufficient disintegration and dissolution means that the moldings disintegrate or dissolve in the buccal cavity in appx. 1 to 120 seconds preferably with in 1 to 60 seconds and more preferably with in 1 to 40 seconds.

Mizumoto et al., [2, 3] have classified sugar-based excipients into two types based on their mouldability and dissolution rate.

Type I saccharides (e.g., lactose and mannitol) exhibit low moldability but high dissolution rate.

Type II saccharides (e.g., maltose and maltitol) exhibit high moldability but low dissolution rate. .(Shukla *et al.*: Sci Pharm. 2009; 76; 309–326).

Moldability is defined as the capacity of the compound to be compressed/ molded and to dissolve. It does not refer to the formation of a true mold by melting or solvent wetting process.

The moldability of Type I saccharide can be improved by granulating it with a Type II saccharide solution. The above technology forms the basis of WOWTAB [5] which involves the use of fluidized bed granulation for the surface treatment of Type I saccharide with Type II saccharide.

This technique has been used in the production of Benadryl Fast melt tablets. Here, two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate [7]. Due to its significant hardness, the WOWTAB formulation is more stable to the environmental conditions than the Zydis or Orasolv and is suitable for both conventional bottle and blister packaging.

The taste masking technology utilized in the WOWTAB is proprietary and claims to offer superior mouth feel due to the patented smooth-melt action [5]. In the process of granulation, low moldable sugar was coated with high moldable sugar followed by a specific humidity treatment, to achieve fast disintegration. The resulting tablet had a hardness of **1.0–2.0 kg** (tablet-size dependent) and presented a preferable disintegration

time of 1–40 secs. Various classes of drugs can be incorporated into the above sugar combination to achieve a MDT with optimum performance characteristics.

A preferable ratio of **5–10% w/w of high moldable sugar** was found to be sufficient to achieve the desired hardness and disintegration property A series of experiments had been conducted to develop a MDT using a combination of starch/cellulose and one or more water-soluble saccharides [32]. Erythritol was found to be the best saccharide because it displayed rapid disintegration, good tolerability, sweetening and a refreshing mouth feel due to its negative heat of solution.

Recently, the Ziplet technology was developed, which can be used for water insoluble drugs or drugs as coated micro particles. It was found that the addition of a suitable amount of a water-insoluble inorganic excipient combined with one or more effective disintegrants imparted an excellent physical resistance to the MDT and simultaneously maintained optimal disintegration even at low compression force and tablet hardness [26]. In fact, breakage of the tablet edges or formation of powder during manufacturing and opening of the blister pack is avoided because of its superior mechanical resistance. The use of water-insoluble inorganic excipients also offers better enhancement of disintegration characteristics in comparison to the most commonly used water-soluble sugars or salts. In fact, tablets composed primarily of water-soluble components often tend to dissolve rather than disintegrate, resulting in much longer disintegration time. As the soluble components dissolve on the tablet's outer layer, a concentrated viscous solution is formed, which reduces the rate of water diffusion into the tablet core

1.7 TYPES OF GRANULATION BY WOW TEHNOLOGY:

1. An active ingredient added to a low moldability saccharide and the resulting mixture is granulated with a high moldability saccharide
2. A low moldable saccharide is granulated with a high moldable saccharide. The resulting granules are mixed with an active ingredient, and the resulting mixture is subjected to compression.
3. A low moldability saccharide is granulated with high moldabilty saccharide to obtain granules. Separately active ingredient is granulated with high moldability saccharide to obtain granules. These granules are mixed and subjected to compression.
4. A low moldability saccharide is granulated with both of an active ingredient and a high moldability saccharide in any order. The resulting are granules are subjected to compression.
5. A low moldability saccharide (central core) is coated with a high moldability saccharide (first layer) and then coated with an active ingredient (second layer), and the resulting product is granulated with a high moldable saccharide (third layer). The resulting granules are subjected to compression.
6. A low moldability saccharide is coated with an active ingredient and the coated product is granulated with a high moldability saccharide. The resulting granules are compressed.

   The active ingredient may be used in an amount of 50% (w/w) or less preferably 20%w/w or less because of total solid components.

   The blending ratio of high moldable saccharide to low moldable saccharide of from 2 to 20% by weight preferably from 5 to 10% by weight.

1.7 ADDITIVES USED IN WOW TECHNOLOGY:

Various additives can be added to the formulation as long as they do not spoil the effects of present invention. They include

1. Disintegrating agents
2. Binding agents
3. Souring agents
4. Vesicants
5. Artificial sweeteners
6. Perfumes
7. Lubricants
8. Coloring agents

1.7.1 DISINTEGRANTS USED IN FAST DISSOLVING TABLETS:

Some patents use effervescent couples as their disintegrant, while others use a combination of disintegrants. Dobetti summarized different types of non-effervescent disintegrants used in the pharmaceutical area.

• **Starch and modified starches.** This group includes natural starches (such as maize Starch and potato starch), directly compressible starches (such as starch 1500), Modified starches (such as carboxymethylstarches and sodium starch glycolate), and starch derivatives (such as amylose).

• **Cross-linked polyvinyl pyrrolidone**

• **Modified celluloses** such as cross-linked sodium carboxymethylcellulose

• **Alginic acid and sodium alginate**

• **Microcrystalline cellulose**

• **Methacrylic acid-divinylbenzene copolymer salts**

In addition, poly (acrylic acid) **super porous hydrogel (SPH)** micro particles were recently reported as super disintegrants possessing a unique porous structure. They were used as wicking agents to decrease the disintegration time of FDTs. The poly (acrylic acid) SPH

micro particles can swell approximately 80 times in distilled water and 50 times in pH 6.8 0.2 M phosphate buffer. The SPH micro particle size had a significant effect on the disintegration time and tensile strength of ketoprofen FDTs. The minimum disintegration time was observed when the microparticle size was in the range of 75–106 μm. Tensile strength of the tablets decreased as the SPH micro particle sizes decreased from 180–250 μm to 25–44 μm. However, when the micro particle sizes were smaller than 25 μm, the tensile strength of the resultant tablets increased as the size decreased. The optimal micro particle size should be in the range of 75–106 μm. The FDTs made of SPH micro particles in the range of 75-106 μm showed the fastest disintegration time (15 ± 2.0 s) and higher tensile strength (84.4 +/- 4.1 N/cm).

1.7.2 Binding agents:

Powdered acacia, gelatin, pullulan etc

1.7.3 Souring agents:

Citric acid, tartaric acid, malic acid

1.7.4 Vesicants

Sodium bicarbonate

1.7.5 Artificial sweeteners

Saccharin sodium, glycyrrhizin, aspartame, stevia, thaumatin.

1.7.6 Perfumes

Lemon, lemon lime, orange, menthol

1.7.7 Lubricants

Magnesium state, sucrose fatty acid esters, polyethylene glycol, talc, stearic acid

1.7.8 Coloring agents

Food dyes, Food Lake dyes, red iron oxide

1.8 COMPACTION AND SUBSEQUENT TREATMENTS

a. Sublimation

The slow dissolution of the compressed tablet containing even highly water-soluble ingredients is due to the fact that the low porosity of the tablets reduces water penetration into the matrix. When volatile materials are compressed into tablets using the conventional method, they can be removed via sublimation, resulting in highly porous structures. The volatile materials include urea, ammonium carbonate, ammonium bicarbonate, hexa methylene tetramine, and camphor. Heinemann disclosed a process to prepare porous tablets by sublimation. The mixtures of volatile adjuvants were made into tablets, which were subsequently heated to remove them. Roser and Blair used vacuum to remove the volatile materials. The full dissolution time was reduced from 10–15 minutes for the tablets formed from trehalose alone to less than 1 minute. In some cases, menthol, camphor, thymol, an organic acid such as adipic acid, and a lower fatty acid such as arachidic acid, capric acid, myristic acid, and palmitic acid were used as the volatile materials, and the sublimation temperature ranged from 40 to 60C. The disintegration time in the human mouth was claimed to be about 25 seconds. Lo disclosed an efficient method for preparing high-strength, highly porous, fast-dissolving delivery devices. In this method menthol, a water-soluble, menthol soluble polymer, and an active ingredient are mixed at a temperature that insures that the menthol is substantially molten. The formulation is disposed in a mold and solidified, and the menthol is sublimed from the solidified molded formulation. Preferably, the solidification occurs at a temperature sufficient to provide a substantially amorphous menthol structure.

b. Humidity Treatment

The mechanical strength of some tablets increased substantially after moisture treatment, compared with the tablets before the treatment. The increase is known to be due to the formation of liquid bridges in the presence of moisture and then formation of solid bridges after drying. As shown in Figure 5, when solid particles start to pick up moisture from the atmosphere, the water is adsorbed onto the surface (A), and then water molecules form a film on it with the vapor pressure over the adsorbed moisture layer equal to Pb (B). The solid starts to dissolve into the adsorbed moisture layer, and the dissolution of solid in the adsorbed

moisture will lead to a decrease in the vapor pressure Pb (C). The decrease in Pb is effectively off set by the increase in temperature of the film (and the solid) caused by the heat released on condensation of the water vapor. The moisture sorption occurs spontaneously, and the thickness of the condensate film grows as long as Pa > Pb. The solid continues to dissolve and saturate the film, maintaining the vapor pressure over the adsorbed moisture layer (Pb). After drying, a solid bridge is believed to occur and increase bonding between the particles (D).

It is also known that certain types of sugar change from the amorphous to the crystalline state when their solution is spray dried or used as a binder solution. Further investigations have shown that when an amorphous sugar is treated to go through the humidification and drying process, it changes to a crystalline state. This change increases the tablet strength substantially. The conceptual process of structural changes of amorphous sucrose to crystalline sucrose is shown in Figure 6.

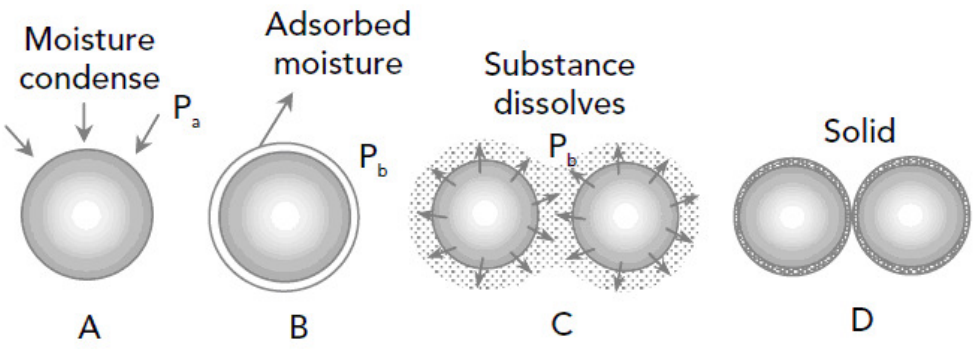


FIGURE 5 A moisture sorption model explaining the increase mechanical strength of FDTs.

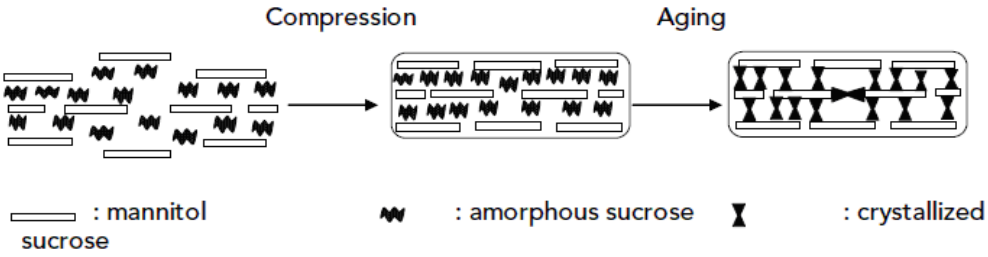


FIGURE 6 A model describing the increase in tablet strength by transformation of amorphous sucrose to crystalline sucrose upon storing under a certain relative humidity.

In a patent by Mizumoto et al.,[2, 3, 4] a drug, a sugar, and an amorphous sugar capable of transforming from amorphous to crystalline state were mixed and compressed into tablets. After the tablets were formed, they were humidified and dried. The amount of the sugar in the formulation can be adjusted according to the drug content and tablet size. The "amorphous sugars" are those that can form an amorphous state by spray drying, freeze drying, or other granulation methods. These amorphous sugars include glucose, lactose, maltose, sorbitol, trehalose, lactitol, and fructose. The relative humidity is determined by the apparent critical relative humidity of the mixture of a drug and an amorphous sugar. A relative humidity greater than or equal to the critical relative humidity of this mixture is chosen for the humidity condition. The advantage of using amorphous sugars is that they have low critical relative humidity, so that they can absorb water even at low moisture levels. The crystalline form of the sugars has difficulty in controlling moisture absorption. Moisture absorption of the crystalline form is not sufficient to strengthen the tablets at a low humidity condition. If a high humidity condition is used, tablets may adhere together, causing manufacturing problems. Another advantage of using amorphous sugars is that transformation of the amorphous state to the crystalline state is irreversible. The sugars in crystalline state have a high critical moisture point, so the strengthened tablets are less susceptible to moisture.

Liu et al. disclosed a system for making FDTs by humidity treatment.

The process includes the following steps:

(1) a water-soluble polymer was used as a binder solution to granulate active ingredients and other excipients, such as low moldability sugars;

(2) the granules were then compressed into tablets;

(3) the tablets were humidified at relative humidity of about 50–100%; and

(4) the tablets were dried.

The hardness of the tablet was about 0.5–12.0 kilo pounds, and the in vivo disintegration time was claimed to be about 1–40 seconds.

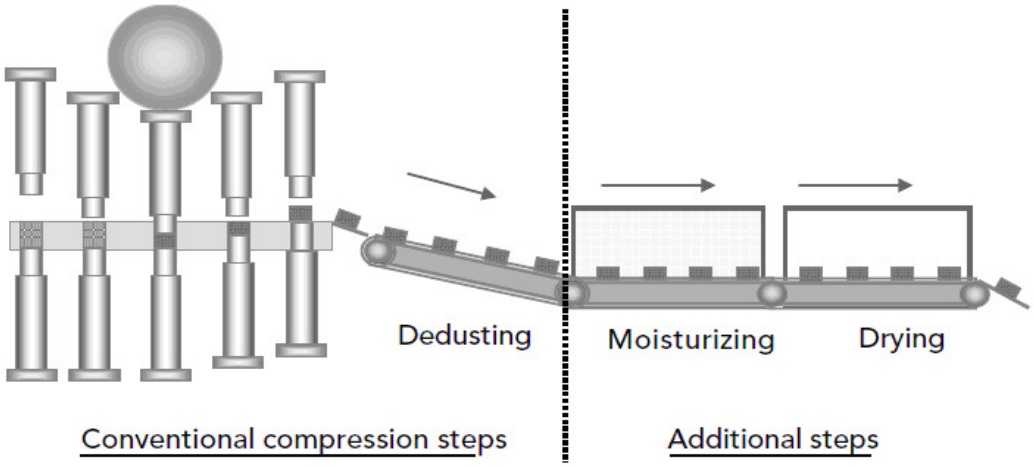


FIGURE 7 Schematic view of the manufacturing apparatus using moisture treatment. The left side of a dotted line shows the conventional compression and dedusting steps, while the right side shows the additional step requiring special chambers for moisture treatment and drying.

Tatara et al. also used moisture treatment and devised an apparatus to handle the fragile tablets before moisture treatment. An active ingredient and other excipients were compressed in low pressure, and then the resultant tablets were moisturized and dried to produce a porosity between 20 and 40%. As shown in Figure 7, the manufacturing apparatus includes a rotary punch-press, a relay conveyor for transferring tablets, a moisturizing section, a drying

section, and a delivery conveyor. In the moisturizing section, the condition was set to allow tablets

Moisturized at 45 ºC, 95% relative humidity for 60 seconds. In the drying section, the temperature was set to 50 ºC for 60 seconds. With this apparatus the fragile tablets before moisture treatment were gently transferred throughout the process.

c. Sintering

Lagoviyer et al. disclosed a process that increased tablet strength by sintering the tablet components at high temperatures and then re solidifying them at lower temperatures. The components in this formulation include bulk agents, structure agents, solvent, and binding agents. A bulk agent in this formulation is used to provide bulk volume to the overall tablet, and suitable agents include carbohydrates, calcium carbonate, and magnesium carbonate. The suitable structure agents should provide a porous support structure to allow quick dissolution of the tablets in the mouth. The structural agents include agar, gelatin, albumin, and chondroitin. Bulking and structural agents were dissolved in a suitable solvent, and the dissolved mixture was spray dried or dispersed to obtain a bead or granulated product with a low density. Choice of the solvent is based on its ability to provide a desired porosity to the bead or granulated product upon drying. Solvents can be chosen from water, ethyl alcohol, isopropyl alcohol, or a mixture thereof. The binders need to melt at the sintering stage, form bonding among granules, and re solidify as the temperature of the final sintering or heating step decreases. Binders are water soluble polymers such as poly(ethylene glycol) (PEG), with a molecular weight of approximately 1000 to 1,000,000. PEG melts at 50–90 ºC, PEG has the advantage of functioning both as a binder and as a capillary attractant. The amount of binding polymer ranged from 0.5% to 25% of the weight of the final product. The binding agents and active ingredients can be introduced to the formulation in several ways. A binding agent and active ingredient can also be dry blended to the spray-dried or dispersed granulated product. They can alternatively be dissolved into solvent with bulking agent and spray dried into granules. The granules are then lightly compressed to form tablets. These tablets are heated for a sufficient time and temperature to allow the binding agent to melt. The heating step is intended to melt the binding agent to create intra-tablet bonds and help weld the product shape together. Typically, a laboratory oven is set at around 50–100 ºC, The heating time ranges from 3 to 45 minutes. The binding agents are re solidified as the temperature is reduced to ambient temperature. The disintegration time is generally within 3–60 seconds.

The heat treatment or sintering step in the patent improved the product's strength and durability. Because the active ingredient can be introduced into the formulation in several ways, taste-masking technologies can be easily incorporated into the process. The dosage form allows the incorporation of a wide range of dosage levels. Because of the high temperature treatment, when heat-labile drugs are incorporated in the formulation, careful attention should be given in this process. The advantages and disadvantages of the technologies describe here are summarized in Table 6. These technologies are commonly applied to the production and development of FDTs.

Advantages of WOWTAB technology:

- Smooth melt action in the mouth because of use of saccharides
- Sufficient hardness suitable for both blister packing and bottle packing
- Special taste masking technology is not necessary unless the drug is highly bitter
- Enhanced patient compliance because of ease of administration

1.9 ODT Evaluation of Special Concern

Crushing strength and friability can be assessed as stated in pharmacopoeias. But some tests are of special concern and these include the following:

Wetting time

Wetting time of dosage form is related to the contact angle. It needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. For this purpose, a tablet is placed on a piece of tissue paper folded twice and kept in a small Petri dish (ID = 6.5 cm) containing 6 ml of water, and the time for complete wetting is measured**.**

Disintegration test

The time for disintegration of ODTs is generally less than one minute and actual disintegration time that patient can experience ranges from 5-30 seconds. The standard procedure of performing disintegration test for these dosage forms has several limitations and they are not suitable for the measurement of very short disintegration times. The method needs to be modified for ODTs as disintegration is required without water; thus the test should mimic disintegration in salivary contents. A modified dissolution apparatus is applied to an ODT with a disintegration time that is too fast to distinguish differences between tablets when the compendial method is used. A basket sinker containing the tablets is placed just below the water surface in a container with 900 mL of water at 37 ^{0}C, and a paddle rotating at 100 rpm is used. The disintegration time is determined when the tablet has completely disintegrated and passed through the screen of the sinker**.** Various scientists have developed new *in vitro* methods that allow an accurate determination of disintegration test. The disintegration test is performed using a texture analyzer instrument. In this test, a flat-ended cylindrical probe penetrates into the disintegrating tablet immersed in water. As the tablet disintegrates, the instrument is set to maintain a small force for a determined period of time. The plots of some distance traveled by the probe generated with the instrument's software provide disintegration profile of the tablets as a function of time. The plot facilitates calculation of the start and end-point of the tablet disintegration.

Dissolution test

The development of dissolution methods for ODTs is comparable to the approach taken for Conventional tablets, and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent ODT. Other media such as 0.1 M HCl and buffer (pH 4.5 and 6.8) should be evaluated for ODT much in the same way as their ordinary tablet counterparts. It has been suggested that USP 2 paddle apparatus is the most suitable and common choice for orally disintegrating tablets, with a paddle speed of 50 rpm commonly used.

Moisture uptake studies

Moisture uptake studies for ODT should be conducted to have an insight into the stability of the formulation, as several excipients used are hygroscopic. Ten tablets from each formulation are kept in a desiccator over calcium chloride at 370C for 24 h. The tablets are then weighed and exposed to 75% RH at room temperature for two weeks. The required humidity (75% RH) is achieved by keeping saturated sodium chloride solution at the bottom of the desiccator for three days. One tablet as control (without superdisintegrant) is kept to assess the moisture uptake due to other excipients. Tablets are weighed and the percentage increase in weight is recorded

1.10 Packaging of ODT

Packing is one of the important aspects in manufacturing ODT. The products obtained by various technologies vary in some of the parameters especially in mechanical strength to a good extent. The products obtained by lyophilization process including various technologies such has Zydis, Lyoc, Quicksolv, and Nanocrystal are porous in nature, have less physical resistance, sensitive to moisture, and may degrade at higher humidity conditions. For these reasons products obtained require special packing. Zydis units are generally packed with peelable backing foil. Paksolv is a special packaging unit, which has a dome-shaped blister, which prevents vertical movement of tablet with in the depression and protect tablets from breaking during storage and transport, which is used for Orasolv tablet. Some of the products obtained from Durasolv. WOW Tab, Pharmaburst oraquick, Ziplets, etc. technologies have sufficient mechanical strength to withstand transport and handling shock so they are generally packed in push through blisters or in bottles.

1.11 Patient counseling in effective use of ODT

ODT developed offers significant advantages for various group of patients, but the majority of patients receiving ODT have little understanding of this novel dosage form. Patients receiving ODT may be surprised when tablets begin to disintegrate/dissolve in mouth. As pharmacists are ideal persons to know about the recent technologies, thus have opportunity to educate the patients for effective treatment.

Counseling of patients about this dosage form can avoid any confusion and misunderstanding in taking ODT. Patient information that needs to be provided includes:

- Storage of this dosage form as some of ODT developed may not have sufficient mechanical strength, which needs to be handled carefully.

- Patients with Siogren's syndrome or dryness of mouth or who take anti cholinergic drugs may not be suitable candidates for administering ODT. Although no water is required to allow drug to disperse quickly and efficiently but decreased volume of saliva may slow the rate of disintegration/dissolution and may reduce the bioavailability of the product.

- Patients need to be clearly told about the difference between effervescent and ODT. Some of technologies use effervescence, which experience a pleasing tingling effect on the tongue.

- Although chewable tablets are available in market and patient need to be counseled about differences between chewable and ODT tablets. This ODT can be used easily in children who have lost their primary teeth and in geriatric patients who have lost their teeth permanently.

With the pharmacists counseling, intervention and assistance about ODT, all patients receiving this novel dosage form could be more properly and effectively treated with greater convenience

II. RESEARCH ENVISAGED

2.1 Need for Study

The research can be seen as work that tries to find new products and processes or to improve existing one. The ultimate object of any research done in the field of pharmaceuticals is to serve the society's need by developing a formulation that is highly efficient. For this research to be successful, the work to be done should be logically and properly planned based on the literature surveyed.

The term solid dispersion refers to a group of solid products consisting of atleast two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles or in crystalline particles. Confusingly, in various studies the designation of solid dispersion is based on the method of preparation. However, since different preparation methods can result in the same subtypes or similar preparation methods can result in different subtypes, it can be argued that solid dispersions should preferably be designated according to their molecular arrangement. Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersion. Therefore, it is essential to use terms that indicate the molecular arrangement in the solid dispersion. Knowledge about the molecular arrangement will enlarge comprehension of the properties and behavior of solid dispersions. The mechanism underpinning dissolution of solid dispersions is poorly understood. A question like, "is the drug present as crystalline phase or as amorphous molecularly dispersed throughout the matrix" is rarely discussed.

Finally, the influence of drug load and method of preparation on dissolution behaviour and stability of solid dispersions can only be understood and predicted when the relation between these characteristics and the mode of incorporation is known.

The focus of the current study is firstly to enhance the solubility of Fenofibrate by solid dispersion technique and to study solid state, drug carrier interactions and to prevent re crystallization of drug from solid dispersions. Secondary objective is to formulate an oral

disintegrating tablet to enhance the drug release and to provide a smooth melt action in the mouth and finally evaluate the tablets dissolution profile.

III. LITERATURE REVIEW

3.1 Literature Review of Fenofibrate

The primary drug information about Fenofibrate was researched from various well known sources like Physicians' Desk Reference (PDR), Rx list, American Society of Health System Pharmacists, American Hospital Formulary Service. An attempt was made to compile the research works reported in the versions scientific journals and advent text books on Solid dispersion technology.

Fenofibrate belongs to antihyperlipidemic class. It causes the decrease in the levels of low density lipoproteins(LDL), and very low density lipoproteins(VLDL), and increases the levels of high density lipoproteins(HDL).

- **Luis Brito et al.,(2006);** has studied the effect of powder processing on performance of Fenofobrate oral disintegrating tablets to find the effect of blending and jet milling of the drug alone and with the excipients on the disintegration time and the release profile of the fenofibrate

- **P. Srinarong et al.,(2009);** were studied the dissolution profile of naproxen in binary and ternary solid dispersions of PEG (4000,6000,20000) with or without non ionic and anionic surfactants prepared by melting method. They found better dissolution from ternary systems than from binary systems since in the former the wetting and solubilizing effects of surfactant and polymer were additive.

- **Shahla Jamzad et al.,(2006);** has studied the role of Surfactant and pH on Dissolution Properties of Fenofibrate. It was concluded that Fenofibrate is a lipophilic compound and practically insoluble in water. Hence, dissolution study of fenofibrate dosage forms necessitates modifications in the dissolution medium to increase the solubility. Having no ionizable group, fenofibrate solubility was not influenced by changes in medium pH. However, the addition of surfactants is a reasonable approach, which if implemented correctly can approximate the GI fluid condition.

- **Ming-Thau Sheu et al.,(2002);** has done the Characterization and dissolution of fenofibrate solid dispersion systems with PEG 6000 and PVP. The effect of co solvency and particle size on the dissolution profile has been studied and dissolution rate was decreased with increase in PEG 6000 concentration and decrease in particle size.

- **D Law et al.,(2008);** has. Investigated the physicochemical and biopharmaceutical characteristics of fenofibrate in amorphous and eutectic solid dispersions with PEG 8000 and PVP K 17. The *in vivo* performance of the two systems showed that the eutectic PEG system achieved a greater AUC than the amorphous PVP system. It was concluded that lipophilic compound can form both amorphous and eutectic solid dispersions with different polymers

- **Payam Zahedi et al.,(2006);** characterize physicochemical parameters affecting the formation of solid molecular dispersions of poorly water soluble drugs in poly(2-hydroxyethyl methacrylate) hydrogels and to investigate the effect of storage humidity levels on their physical stability. Samples were prepared by an equilibrium solvent loading process, the results show that a threshold drug loading level of about 30%, above which transition from amorphous to crystal was observed and also found enhanced dissolution rate than pure drug.

- **Ledjan Malaj et al.,(2010):** assessed the physical interaction between several aryl propionic acid derivatives and polyvinyl(pyrrolidone)k30 stored together ar 298K at different releative humidities(RH 55,75,86%). They found, hydration of drug-PVP mixtures had important repercussion on drug solubility and intrinsic dissolution rate(IDR). In general, an increase in water solubility and consequently an increase in IDR were observed, with few exceptions, at highest RH%.

- **Samer al-dhalliet al.,(2007);** studied the potential of solid dispersion-based formulation using Gelucire 44/14 as a carrier to enhance the dissolution and oral bioavailability of fenofibrate, PEG 400 was added to lower the melting point of matrix and *In vivo* evaluation of fenofibrate-Gelucire 44/14 solid dispersion

containing polyethylene glycol (PEG) 400 showed that the extent of drug absorption, expressed as AUC0-∞, was increased by approximately 60% over that of micronized fenofibrate

- **Tejas Patel et al.,** has studied the enhancement of dissolution of Fenofibrate by Solid dispersion and lyophilization technique using PEG 6000, Poloxamer 407 and a mixture of PEG 6000 and Poloxamer 407(1:1 mixture). The effect of melt and solvent methods of preparation of solid dispersion on dissolution behavior was also investigated. The dispersion containing six parts of the PEG 6000: Poloxamer 407 mixture (PEG 4000/PEG 6000, 1:1 mixture) showed a 12-fold increase in D60 as compared with pure drug

- **BASF** the chemical company has characterized the graft polymer Soluplus with Fenofibrate as a Fenofibrate and the solubility of the drug has been significantly enhanced in the 1:4 ratio of drug and polymer by hot melt extrusion method.

- **Christian Leuner et al.,(2000);** Review article improving drug solubility for oral delivery using solid dispersions.

- **Ruchi Tiwri et al.,(2009);** Solid dispersion: An overview to modify bioavailability of poorly water soluble drugs. International Journal of pharm Tech Research vol.1,no.4, pp 1338-1349.

- **Dhirendra K et al.,(2009);** Solid dispersion: A Review Pak.J.Pharm.Sci, Vol.22. No.2,.april 2009, pp, 234-246.

- **Patidar Kalpana et al.,(2010);**Solid dispersion: Approaches, Technology involved, Unmet need& challenges. Drug Invention Today Vol,2.Issue 7.July 2010.

- **V.Kamalakkannan et al., (2010);** Solubility enhancement of poorly soluble drugs by solid dispersion technique-A review. Journal of Pharmacy Research 2000,3(9),2314-2321.

- **Raja rajeswari. K et al., (2011);** were prepared solid dispersion by hot melt extrusion of Valsartan with soluplus. They found 1:9 ratio of drug and soluplus showed 100% drug release from solid dispersion.

- **Ravi Kumar et al., (2009);** has done the Formulation Evaluation of Mouth Dissolving Tablets of Fenofibrate Using Sublimation Technique using camphor, thymol, ammonium bicarbonate and different concentrations of menthol using direct compression method. menthol at 12.5% concentration have shown quick disintegrating features, i.e., within 20 s, which is very characteristic of orodispersible tablets. The *in vitro* drug release study revealed that menthol at a concentration of 12.5 % (F10) of the dosage form weight was able to fast the release of Fenofibrate within 10 minutes

- **Yourong Fu et al., (2004);** *Critical Reviews in* Orally Fast Disintegrating Tablet Developments, Technologies, Taste-Masking and Clinical Studies.

- **Jaysukh J Hirani et al., (2009);** Orally Disintegrating Tablets: A Review

- **Mizumoto T et al., (1996);** Formulation design of a novel fastdisintegrating tablet. Intrabuccally dissolving compressed moldings comprising a saccharide US 5576014

- **Andries. F. Maris et al., (2003);** were studied the effect of compression force, humidity and disintegrant concentration on disintegration and dissolution of furosemide tablets

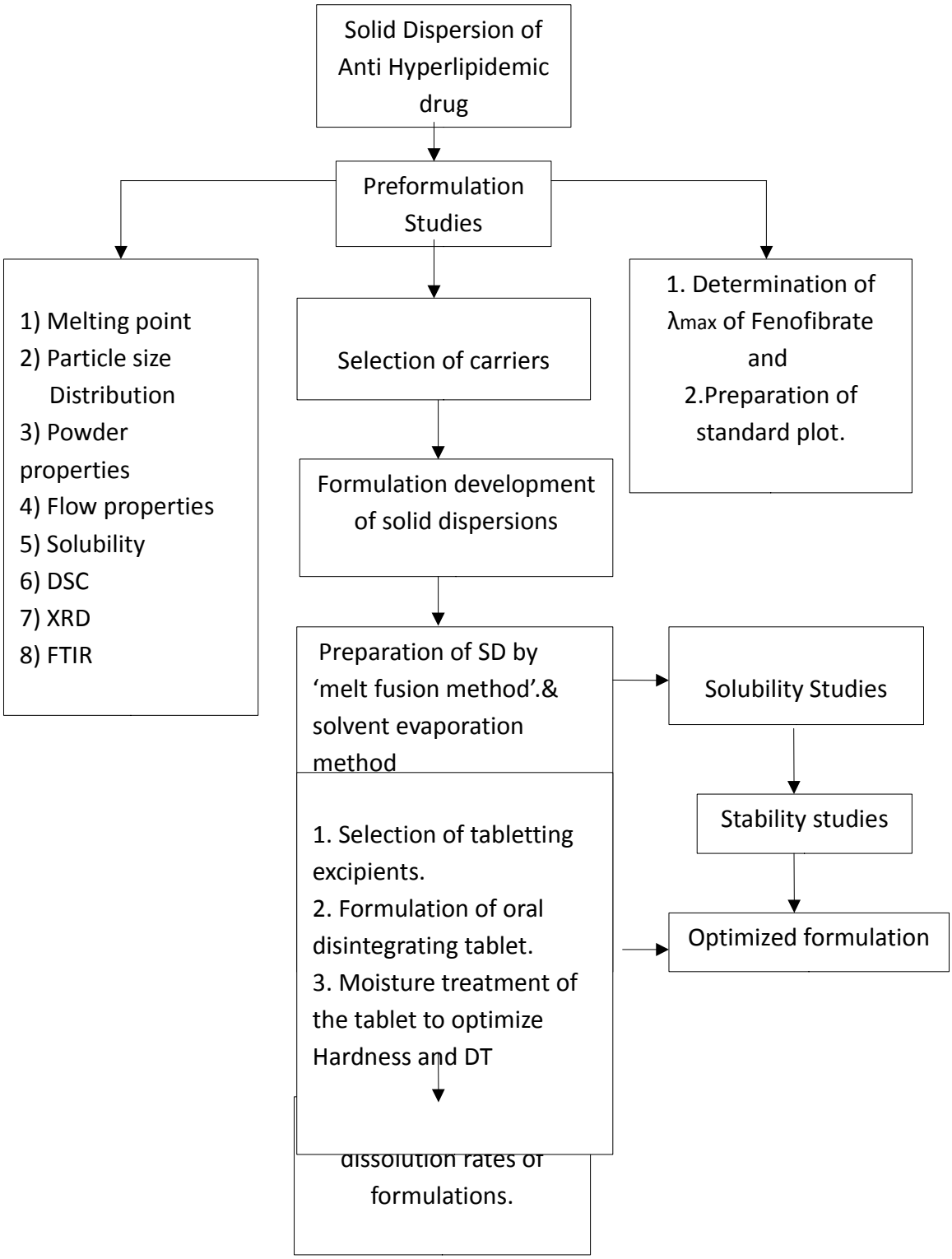
- **Late SG et al.**, has done research on effect of disintegration promoting agent, lubricants and moisture treatment on optimized fast disintegration tablets.

- **Chowhan ZT (1980**) has studied the effect of low and high humidity ageing on the hardness, disintegration time and dissolution rate of Dibasic calcium phosphate based tablets
- **Suresh Bandari et al.,** Orodispersible tablets- An overview

IV. Objective of Study

- To enhance the solubility of Fenofibrate by solid dispersion technique.
- To optimize carrier and carrier concentration in the preparation of solid dispersions.
- To perform solubility of pure drug and solid dispersions.
- To characterize the solid state property of pure drug and solid dispersions by DSC, XRD, FTIR studies.
- To formulate the oral disintegrating tablets through wowtab technology.
- To optimize the moisture treatment of oral disintegrating tablets for attaining sufficient hardness and disintegration time.
- To evaluate the oral disintegrating tablets.
- To perform the stability study for optimized oral disintegrating tablets.

V. Plan of Work



VI. LIST OF EQUIPMENTS AND MATERIALS USED

Table 8: List of Equipments Used

S.No.	Name of the Equipment	Model	Supplier
1	Mechanical stirrer	RZR 2102 control	Heidolph
2.	Electronic weighing balance	BBA422-3SM	METTLER TOLEDO USA
3.	Disintegration Test apparatus	ED-2AL	ELECTROLAB
4.	Friabilator	EF/W	ELECTROLAB
5.	Laboratory oven	DTC-00R	NEWTRONIC
6.	Compression machine	CMD4	cadmach
7.	Stability chamber	-	thermolab scientific equipments
8.	Tablet hardness tester	Tablet tester 8M	pharmatron Dr. Schleuniger
9.	Induction cap sealear	CsP 300	Sigma CapSeal
10.	UV-Shimadzu	UV-2450	SHIMADZU
11.	Quadraco mill	197 S	GANSONS LTD
12.	Sieves	-	Retsch Solutions in Milling & Sieving
13.	DSC	822 e	METTLER TOLEDO
14.	XRD		BRUKER
15.	FTIR	Spectrum	PerkinElmer precisely
16.	Dissolution apparatus	TDT-08L	ELECTROLAB
17.	Vernier calipers	CD-6"CS	Mitutoyo Japan
18.	Tap density meter	ETD-1020	ELECTROLAB
19.	pH-Meter	PH720	WTW

Table 9: Excipients employed and their suppliers

S.No.	Excipients	Supplier
1.	API	**Matrix Laboratories Ltd.**

		MATRIX Laboratories Limited
3.	PVP K90	**ISP Corporation** ISP INTERNATIONAL SPECIALTY PRODUCTS
4.	Hydroxy propyl methyl cellulose	**NISSO GROUP**
5.	Soluplus	**BASF** BASF The Chemical Company
6.	Microcrystalline cellulose (Avicel 101)	Signet
7.	Mannitol SD 200	ROQUETTE
8.	Sorbitol	ROQUETTE
9.	Polyplasdone xl	ROQUETTE
10.	Kollicoat IR	BASF The Chemical Company
11.	Hydroxy propyl cellulose (ssl)	**NISSO GROUP**
12.	Magnesium stearate	EVONIK INDUSTRIES

VII. DRUG PROFILE

The drug, belongs to fibrate class. It is used to reduce both low-density lipoprotien (LDL) and very low density lipoprotein (VLDL) levels, as well as increasing high-density lipoprotein (HDL) levels and reducing triglycerides level . It is mainly used in the treatment of hypercholesterolemia. It reduces cholesterol levels in patients at the risk of cardiovascular diseases.

Structure:

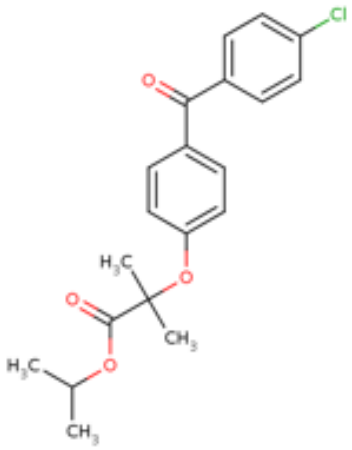


Table 10: Physico – Chemical Properties of drug

Description	White powder
Chemical name	2-[4-(4-chlorobenzoyl) phenoxy] 2-methyl-propanoic acid, 1-methylethyl ester
Molecular formula	$C_{20}H_{21}O_4Cl$
Molecular weight	360.83
Solubility	Insoluble in water; soluble in organic solvents like ethanol, DMSO and DMF .
Melting point	80.5°C
Functional category	In the treatment of hypercholesterolemia i.e. presence of high levels of cholesterol due to abnormalities in the levels of lipoproteins like LDL,VLDL,HDL.
Storage conditions	Store cool, dry place.

7.1 Site and Mode of Action:

The drug exerts its therapeutic effects through activation of peroxisome proliferator activated receptor a (PPARa). This increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III. The resulting fall in triglycerides produces an alteration in the size and composition of LDL from small, dense particles, to large buoyant particles. These larger particles have a greater affinity for cholesterol receptors and are catabolized rapidly.

7.2 Pharmacokinetics of drug:

Absorption:

The absolute bioavailability of the drug cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, after the drug is dissolved, it is well absorbed from the gastrointestinal tract.

Peak plasma levels of Fenofibric acid occur an average of 3-8 hours after administration.

Effect of Food on Absorption

The drug is insoluble in water and its bioavailability is optimized when taken with meals. The extent of absorption of (AUC) is comparable between fed and fasted conditions.

Food increases the rate of absorption of the drug approximately 55%.

Distribution

Volume of distribution is 30L.

Serum protein binding was approximately 99% bound to plasma proteins

Metabolism:

Following oral administration, drug is rapidly hydrolyzed by esterases to the active metabolite; no unchanged drug is detected in plasma of healthy subjects following drug administration. Active metabolite is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of active metabolite is

reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

In vivo metabolism data indicate that neither drug nor active metabolite undergo oxidative metabolism (e.g.cytochrome P450) to a significant extent.

Excretion:

After absorption, drug is mainly excreted in the urine in the form of metabolites.

After administration of radiolabeled drug, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Active metabolite is eliminated with a half-life of approximately 16 hours, allowing once daily administration.

7.3 Interactions:

7.3.1 Drug interactions:

Table 11:Interactions of drug

Drug	**Interaction**
Acenocoumarol	The drug increases the anticoagulant effect
Anisindione	The drug increases the anticoagulant effect
Atorvastatin	Increased risk of myopathy/rhabdomyolysis
Cerivastatin	Increased risk of myopathy/rhabdomyolysis
Dicumarol	The drug increases the anticoagulant effect
Fluvastatin	Increased risk of myopathy/rhabdomyolysis
Lovastatin	Increased risk of myopathy/rhabdomyolysis
Pravastatin	Increased risk of myopathy/rhabdomyolysis
Rosuvastatin	Rosuvastatin possibly increases the effect of the drug
Simvastatin	Increased risk of myopathy/rhabdomyolysis
Warfarin	The drug increases the anticoagulant effect

7.3.2 Food interactions:

Food increases the rate of absorption of the drug.

7.4 Indications and usage:

Drug 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 (Fredrickson Types IIa and IIb). Drug is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Fenofibricacid, the active metabolite of drug, produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with drug results in increases in high density lipoprotein (HDL) and apoproteins apoAI and apoAII.

It is used alone or in conjunction with statins.

7.4.1 Contraindications:

Drug is contraindicated in patients who exhibit hypersensitivity to it.
It is contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.
It is contraindicated in patients with preexisting gallbladder disease

7.4.2 Side effects:

- constipation;
- dizziness or lightheadedness;
- fatigue;
- flu-like symptoms;
- gas;
- headache;
- infection;
- joint pain;
- muscle pain or tenderness;
- rashes;
- runny nose;
- stomach pain;
- upset stomach;
- weakness

7.5. Drug Analysis

7.5.1. Determination of λ_{max}

Procedure:

100mg of pure drug was taken and known concentration of drug solution was prepared by solubilizing in methanol then suitably diluting drug solution in water containing 0.5% sodium lauryl sulphate. The solutions were scanned from 200-400 nm against the reagent blank to fix absorption maxima. Spectrum of the Fenofibrate was obtained and λ_{max} of Fenofibrate was found to be 290 nm. Hence all further investigations were carried out at the same wavelength.

7.5.2. Procedure for Calibration curve

A) Preparation of 0.5% sodium lauryl sulphate solution: 5.0 gms of sodium lauryl sulphate was weighed and added to required quantity of water with slow and continuous stirring for dissolving and to avoid formation of large amount of foam. The prepared solution was sonicated for 45min for complete solubilization of sls in water-

Calibration Curve of Fenofibrate in water

Solutions: 1) Standard Stock -1mg/ml in water+0.5% sls dissolution medium

2) Working Stock - 100mcg/ml in water+0.5% sls dissolution medium

Procedure for plotting standard plot and estimation of drug in by Double Beam UV Spectrophotometer

From the working stock solution, different aliquots were taken in series of 10mL volumetric flasks and volume made up with buffer to get a series of working standard solutions of concentrations, 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml 10µg/ml and 12µg/ml. The absorbance of samples was obtained spectrophotometrically against the reagent blank at 290nm**.** The calibration curves were constructed by plotting drug concentration versus the absorbance value at 290 nm and the regression equation was computed.

7.5.3. Particle size determination: Dry sieve analysis for particle size determination

Dry Sieving Method— each test sieve was sieved to the nearest 0.1 g. An accurately weighed quantity of test specimen was placed on the top (coarsest) sieve, and lid was replaced. The nest of sieves was agitated for 5 minutes. Then each sieve was carefully removed from the nest without loss of material. Each sieve was reweighed, and the weight of material on each sieve was determined. The weight of material in the collecting pan was also determined in a similar manner. The nest of sieves were reassembled and agitated for 5 minutes. Each sieve was removed and weighed, as previously described. Upon completion of the analysis, the weights of material were reconciled. Total losses must not exceed 5% of the weight of the original test specimen.

Principles of Analytical Sieving— Analytical test sieves are constructed from a woven-wire mesh, which is of simple weave that is assumed to give nearly square apertures and is sealed into the base of an open cylindrical container. The basic analytical method involves stacking the sieves on top of one another in ascending degrees of coarseness, and then placing the test powder on the top sieve.

The nest of sieves is subjected to a standardized period of agitation, and then the weight of material retained on each sieve is accurately determined. The test gives the weight percentage of powder in each sieve size range. This sieving process for estimating the particle size distribution of a single pharmaceutical powder is generally intended for use where at least 80% of the particles are larger than 75 µm. The size parameter involved in determining particle size distribution by analytical sieving is the length of the side of the minimum square aperture through which the particle will pass.

PSD of API and solid dispersions were determined using a stack of metal sieve plates from the largest to the finest aperture in the following order: 500, 355, 250, 180, 125, 63 and 45 µm. Retsch apparatus type AS 200 basic was used for the analysis. The weight of the powders retained on the surface of each sieve plate was divided by the total sample weight to obtain the corresponding weight percentage oversize for each sieve fraction.

7.5.4. Solubility studies

Solubility studies were performed by taking drug in 250 mL of buffer and subjected to mechanical shaking at 200 rpm for 2 hrs. The resultant dispersions were collected and filtered through 0.2 µ filters and the concentration of drug was determined from absorbance at 290 nm. The solubility was performed at various pH conditions pH 1.2, pH 4.5, pH 6.8, pH 7.4 and water.

7.5.5 DSC thermogram of Fenofibrate: The solid state characteristics of drugs are known to potentially exert a significant influence on the *solubility parameter.* The utility of solid-state spectroscopy for characterization of polymorphic systems is becoming exceedingly important.

Polymorphs and/or solvates of a pharmaceutical solid can have different chemical and physical properties such as melting point, chemical reactivity, apparent solubility, dissolution rate, optical and electrical properties, vapor pressure, and density. These properties can have a direct impact on the process-ability of drug substances and the quality/performance of drug products, such as stability, dissolution, and bioavailability.

Polymorphic studies of drug and selected carrier were performed by DSC. Melting point of drug, nature of carrier can be determined by this technique. The polymorphic form of drug, carrier were studied. The samples were taken separately in a pierced aluminium crucible with a capacity of 40µL and evaluated in METTLER TOLEDO 822^e equipment using eSTAR software in temperature range of 25-325º C at a heating rate of 10 º C/min with a stream of nitrogen . The thermograms were recorded.

7.5.6. X-Ray Diffraction study of Fenofibrate

Crystallinity of the drug was determined using the Bruker D8 Advance XRD with copper target. The conditions were: 40 Kv voltages; 40 mA current; at room temperature. The drug was loaded on to the diffractometer and scanned over a range of 2θ values from 3^0 to 45^0 at a scan rate of 0.1^0 /sec.

7.5.7. Fourier Transform Infra Red spectrum of Fenofibrate

FTIR was performed by KBr pellet method. Drug and KBr were taken in 1:100 ratio and ground in mortar for even distribution of sample and KBr. Then it was prepared in the form of disk by applying pressure of 5 tons for 5 min using a hydraulic press and subjected to IR. The software used was spectrum (version 6.1.0) in the wave number range of 400-4000 cm^{-1}. The resolution is 4 cm^{-1}.

7.5.8. Powder and Flow Properties of API (USP NF 2009).

A) Bulk density:

Bulk density was determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder (USP *Method I*).

Approximately 10 gms of test sample, M was introduced into 25 ml dry measuring cylinder without compacting. The powder was leveled carefully without compacting and read the unsettled apparent volume V_0, to the nearest graduated unit. Bulk density was calculated, in g per ml, by the formula.

$$(M) / (V_o)$$

Generally replicate determinations are desirable for the determination of this property.

B) Tapped density:

Tapped density was achieved by mechanically tapping a measuring cylinder containing a powder sample. After measuring the initial weight and volume, the cylinder was mechanically tapped, and volume readings were taken until little further volume change is observed.

Procedure: Cylinder containing the sample was tapped mechanically by raising the cylinder and allowing it to drop under its own weight using a suitable mechanical tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. Unless otherwise specified, the cylinder was tapped 500 times initially and the tapped volume was measured, V_a, to the nearest graduated unit. The tapping was repeated for an additional 750 times and the tapped volume was measured, V_b, to the nearest graduated unit. If the difference between the two volumes is less than 2%, V_b is the final tapped volume, V_f. It was repeated in

increments of 1250 taps, as needed, until the difference between succeeding measurements is less than 2%. The tapped density was calculated, in g per mL, by the formula:

$$(M) / (V_f).$$

Generally replicate determinations are desirable for the determination of this property.

C) Compressibility Index:

The Compressibility Index and Hausner Ratio are measures of the property of a powder to be compressed. As such, they are measures of the relative importance of interparticulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the *Compressibility Index* and the *Hausner Ratio.*

Compressibility Index— Calculate by the formula:

$$CI\ (\%) = \frac{V_o - V_f}{V_o} \times 100$$

Hausner Ratio— Calculate by the formula:

$$HR = \frac{V_f}{V_o}$$

Where V_0 - Bulk volume

V_f - Tapped volume

Table 12: Scale of Flowability (USP)

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

D) Determination of Angle of Repose

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles.

Angle of repose was formed on a fixed base with a retaining lip to retain a layer of powder on the base. The base should be free of vibration. The height of the funnel was varied to carefully build up a symmetrical cone of powder. Care should be taken to prevent vibration as the funnel is moved. The funnel height should be maintained approximately 2–4 cm from the top of the powder pile as it is being formed in order to minimize the impact of falling powder on the tip of the cone. If a symmetrical cone of powder cannot be successfully or reproducibly prepared, this method is not appropriate. Angle of repose was determined by measuring the height of the cone of powder and calculating the angle of repose, from the following equation:

$$\tan \alpha = h/r$$

Table 13: Flow Properties and Corresponding Angle of Repose

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

VIII. Excipient profile

POVIDONE

Nonproprietary Names	• BP: Povidone, JP: Povidone, PhEur: Povidonum USP: Povidone
Synonyms	E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; ,polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer
Empirical formula	$(C_6H_9NO)_n$
Molecular weight	2500–3000
Description	Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.
Functional categories	Disintegrant; dissolution aid; suspending agent; tablet binder.
Solubility	freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water;
Melting point	Softens at 150°C.
Stability and storage conditions	Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.
Incompatibilities	It forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds.
Applications	Povidone solutions may also be used as coating agents and it is also used as a suspending, stabilizing, or viscosity-increasing agent In tableting, povidone solutions are used as binders in wet-granulation.

Table no. 14 profile of povidone

MANNITOL

Nonproprietary Names	• BP: Mannitol, JP: D-Mannitol,PhEur: Mannitolum, USP: Mannitol
Synonyms	Ordycepic acid; C*PharmMannidex; E421; manna sugar; D-mannite; mannite; Mannogem; Pearlitol.
Empirical formula	$C_6H_{14}O_6$
Description	Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules.
Functional categories	Diluent; diluent for lyphilized preparations; sweetening agent; tablet and capsule diluent; tonicity agent.
Melting point	166–168°C
Density	1.514 g/cm^3
Stability and storage conditions	Mannitol is stable in the dry state and in aqueous solutions. In solution, mannitol is not attacked by cold, dilute acids or alkalis, nor by atmospheric oxygen in the absence of catalysts The bulk material should be stored in a well-closed container in a cool, dry place.
Incompatibility	Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride. Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation.
Applications	Used as a diluent (10–90% w/w) in tablet formulations, Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available.

Table no. 15: profile of mannitol

MAGNESIUM STEARATE

Nonproprietary Names	BP: Magnesium Stearate, JP: Magnesium Stearate , PhEur: Magnesium Stearate , USP-NF: Magnesium Stearate
Synonyms	Dibasic magnesium stearate; magnesium distearate; magnesiistearas; magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt; Synpro 90
Empirical formula	$C_{36}H_{70}MgO_4$
Molecular weight	591.24
Description	Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.
Functional categories	Tablet and capsule lubricant.
Solubility	Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).
Melting point	117–150 °C
Density	1.092 g/cm3
Loss on drying	46.0%
Stability and storage conditions	Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.
Incompatibilities	Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials.
Applications	It is primarily used as a lubricant in capsule and tablet manufacture.

HYDROXYPROPYL METHYL CELLULOSE:

Nonproprietary Names	• BP: Hypromellose • JP: Hydroxypropylmethylcellulose • PhEur: Hypromellosum • USP: Hypromellose
Synonyms	Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; Tylopur.
Description	Hypromellose is an odorless and tasteless, white or creamy white fibrous or granular powder.
Functional categories	Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent; suspending agent; tablet binder; viscosity-increasing agent.
Solubility	soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol(95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypermellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents
Melting point	browns at 190–200^{0}C; chars at 225–230^{0}C.Glass transition temperature is 170–180^{0}C.
Stability and storage conditions	Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.
Incompatibilities	Hypromellose is incompatible with some oxidizing agents.
Applications	as a matrix for use in extended-release tablet formulations used to enhance the aqueous solubility of poorly soluble compounds by making solid dispersions.

Table no. 17: profile of HPMC

SOLUPLUS:

Nonproprietary Names	Graft co polymer
Molecular weight	90 000 – 140 000g/mol
Description	Soluplus is a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft co-polymer (13/57/30). It is a free flowing white to slightly yellowish granule with faint characteristic odour.
Functional categories	used in film casting, used in capsule formation, as a binder in wet granulation or dry binder in direct compression, drug layering, and as emulsifier
Solubility	It is soluble in water. It is also soluble in acetone (up to 50%), methanol (up to 45%), ethanol (up to 25%) and dimethyformamide (up to 50%)
Glass transition temperature	Approximately 70^0c
Stability and storage conditions	It should be closed in tightly closed container.
Applications	Soluplus is used to increase solubility of poorly soluble drugs, used in extrude formation,

Table no. 18: profile of soluplus

KOLLICOAT IR

Synonyms	Polyvinyl alcohol-polyethylene glycol copolymer.
Molecular weight	about 45,000 Daltons
Description	free-flowing powder, colorless, white, very faint odour

Viscosity (20 % solution)	115 mPas
Composition	Ethanol, polymer with .alpha.-hydro-.omega.-hydroxy poly(oxy-1,2-ethanediyl) CAS-No. 96734-39-3
Functional categories	Coating agent; film-former; tablet binder;., Dissolution enhancer
Solubility	Solubility water > 50 % 0.08 N HCI > 50 % phosphate buffer pH 6.8 > 50 % pH (20 % solution) 6.7
Melting point	Melting temperature 209 °C
Stability and storage conditions	Store in cool place. Keep container tightly closed in a dry and well-ventilated place. Provide appropriate exhaust ventilation at places where dust is formed. Normal measures for preventive fire protection.
Incompatibilities	Strong oxidizing agents.
Applications	as a matrix for use in immediate-release tablet formulations. used to enhance the aqueous solubility of poorly soluble compounds by making solid dispersions.

Table no. 19: profile of kollicoat

SORBITOL

Synonyms	glucitol, Sorbogem® and Sorbo
Molecular weight	182.17 g mol^{-1}
Molecular formula	$C_6H_{14}O_6$
Description	free-flowing powder, colorless, white, very faint odour

Density	1.489 g/cm³
Composition	sugar alcohol that the human body metabolizes slowly. It can be obtained by reduction of glucose, changing the aldehyde group to a hydroxyl group
Functional categories	Sweetner, laxative, Humectant, thickener
Solubility	Easily soluble in cold water, hot water.
Melting point	95 °C, 368 K, 203 °F
Boiling point	296 °C, 569 K, 565 °F
Stability and storage conditions	Keep container dry. Keep in a cool place. Ground all equipment containing material. Keep container tightly closed. Keep in a cool, well-ventilated place. Combustible materials should be stored away from extreme heat and away from strong oxidizing agents..
Incompatibilities	Strong oxidizing agents.
Applications	Sweetner, humectant and thickener in health care, food and cosmetics

POLYPLASDONE XL

Synonyms	Crospovidone, Polyvinylpyrrolidone.
Molecular weight	about 45,000 Daltons

Description	Non-ionic, crosslinked, White, free flowing, compressible powder
pH(10 %slurry)	5.0 – 8.0
Composition	A synthetic homopolymer of cross-linked N-vinyl-2-pyrrolidone.
Functional categories	Disintegrant, Solubilizer
Solubility	Completely insoluble in water, acids, alkalis, and all organic solvents. Hygroscopic. Swells rapidly in water. Rapidly disperses in water, but does not gel even after prolonged exposure.
Melting point	Not available
Stability and storage conditions	Store in cool place. Keep container tightly closed in a dry and well-ventilated place. Provide appropriate exhaust ventilation at places where dust is formed. Normal measures for preventive fire protection.
Incompatibilities	Strong oxidizing agents.
Applications	Super disintegrant and dissolution aid in wet granulation, dry granulation and direct compression.

Table no. 21: profile of PPXL

HYDROXY PROPYL CELLULOSE (SSL)

Synonyms	Cellulose, 2-hydroxypropyl ether; oxypropylated cellulose.
Molecular weight	Variable

Description	White, free flowing, compressible powder
Viscosity	Lowest viscosity, varies based on the specific use
Composition	Nisso HPC consists of hydroxypropyl ethers obtained by the reaction of cellulose with propylene oxide.
Functional categories	It is used as a topical ophthalmic protectant and lubricant.
Solubility	Soluble in both water and organic solvents.
Melting point	Variable
Stability and storage conditions	Store in cool place. Keep container tightly closed in a dry and well-ventilated place. Provide appropriate exhaust ventilation at places where dust is formed. Normal measures for preventive fire protection.
Incompatibilities	Strong oxidizing agents.
Applications	available for food use as a fat substitute, whipping aid, emulsion aid, and for film coating and tablet binding. .

Table no. 22: profile of HPC SSL

LACTOSE MONOHYDRATE

Nonproprietary Names	BP: Lactose monohydrate PhEur: Lactosum monohydricum JP: Lactose USPNF: Lactose monohydrate
Synonyms	CapsuLac; GranuLac; Lactochem; lactosum monohydricum;Monohydrate; Pharmatose; PrismaLac; SacheLac; SorboLac;SpheroLac; SuperTab 30GR; Tablettose
Empirical formula	$C_{12}H_{22}O_{11}$_H_2O
Molecular weight	360.31
Description	Lactose occurs as white to off-white crystalline particles or powder. Lactose is odorless and slightly sweet-tasting
Functional categories	Binding agent; diluent for dry-powder inhalers; tablet binder; tablet and capsule diluent.
Solubility	Chloroform Practically insoluble Ethanol Practically insoluble Ether Practically insoluble Water 1 in 5.24 1 in 3.05 at 40^0C 1 in 2.30 at 50^0C 1 in 1.71 at 60^0C 1 in 0.96 at 80^0C
Melting point	201–202^0C
Density	1.545 g/cm3
Loss on drying	40.5%
Stability and storage conditions	Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions. Solutions show mutorotation. Lactose should be stored in a well-closed container in a cool, dry place.
Incompatibilities	A Millard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. Lactose is also incompatible with amino acids, aminophylline, amphetamines, and lisinopril.
Applications	Lactose is widely used as a filler or diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas.

Table no. 23: profile of lactose

IX. METHODOLOGY

9.1. Formulation Development of Solid Dispersions

A).Preparation of Solid Dispersion by Solvent Evaporation Technique:

The carriers used in the study were soluplus, PVP K90, HPMC 3cps, kollicoat IR, HPS SSL. In the preparation of solid dispersion by solvent evaporation method, solvent used was methanol which dissolves both drug and carriers.

Solid dispersions were prepared in drug/carrier concentrations of 1:1, for drug: soluplus/ PVP K90/ HPMC 3cps/ kollicoat IR/ HPS SSL and after characterization drug carrier concentrations of 1:0.5, 1:1,1:2, 1:3, 1:4 for drug : HPMC 3cps and soluplus were prepared. Drug is initially dissolved in solvent and then carriers were added to the solution under stirring conditions. Then the solvent is subjected to evaporation. After complete evaporation of the solvent, solid dispersion is collected, milled, dried and passed through 60# size. The obtained solid dispersions were further characterized for drug content, Solubility studies and DSC

B).Preparation of Solid Dispersion by Melt fusion Technique:

Solid dispersions were prepared in drug/carrier concentrations of 1:0.5, 1:1, 1:2, 1:3, 1:4 for drug: HPMC 3cps and drug: soluplus. Melt fusion is carried out in an oil bath. Drug and polymer in specific ratios are initially premixed and sifted through sieve no 40 and the mixture is transferred in to the oil bath.

The temperature was set above the melting point of drug and the mixture was continuously mixed at that temperature until drug melts and completely dispersed in the polymer

The resulting mixture in the glassy state was subjected to quench cooling in an ice bath and the dispersion is milled, dried and sifted through sieve no 60. The obtained solid dispersions were further characterized for drug content, Solubility studies and DSC

Table 24: Composition of solid dispersions

Formulation code	Carrier	Ratios
SD1	Drug: PVP K90	1:1
SD2	Drug: soluplus	1:1
SD3	Drug: kollicoat IR	1:1
SD4	Drug: HPC SSL	1:1
SD5	Drug: HPMC 3cps	1:1
SD6	Drug: soluplus	1:0.5
SD7	Drug: soluplus	1:1
SD8	Drug: soluplus	1:2
SD9	Drug: soluplus	1:3
SD10	Drug: soluplus	1:4
SD 11	Drug: soluplus fusion method	1:0.5
SD 12	Drug: soluplus fusion method	1:1
SD 13	Drug: soluplus fusion method	1:2
SD 14	Drug: soluplus fusion method	1:3
SD15	Drug: soluplus fusion method	1:4
SD16	Drug: HPMC 3cps	1:0.5
SD17	Drug: HPMC 3cps	1:1
SD18	Drug: HPMC 3cps	1:2
SD19	Drug: HPMC 3cps	1:3
SD20	Drug: HPMC 3cps	1:4
SD21	Drug: HPMC 3cps fusion method	1:0.5
SD22	Drug: HPMC 3cps fusion method	1:1
SD23	Drug: HPMC 3cps fusion method	1:2
SD24	Drug: HPMC 3cps fusion method	1:3
SD25	Drug: HPMC 3cps fusion method	1:4

9.2. CHARACTERIZATION OF SOLID DISPERSIONS

9.2.1. Drug content estimation

100mg of pure drug was taken and dissolved in approximately 3 ml of methanol. The solution was filtered and the volume of solution was made up with water containing sls, suitably diluted with buffer and drug content was analyzed against blank by UV spectrophotometer at 290nm. Solid dispersions equivalent to 100 mg of drug was transferred to a separate volumetric flask and dissolved in methanol and filtered. Required amount of water was added to the filtrate, suitably diluted and drug content was analyzed against blank by UV spectrophotometer at 290 nm. The percentage of drug present in the solid dispersion was calculated.

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9.2.2. Solid state characterization of solid dispersion by Differential Scanning Calorimetry (DSC)

The solid dispersions were taken in an pierced aluminium crucible with a capacity of 40µL and evaluated in METTLER TOLEDO equipment using eStar software (version 9.10) in a temperature range of 25-325º C at a heating rate of 10 º C/min under a stream of nitrogen. The thermograms were recorded.

9.2.3. Solubility studies

Solubility studies were performed for those solid dispersions that have shown a change in the polymorphic structure (crystalline state to amorphous state) by taking solid dispersions of drug and various carrier ratios in 250 mL of water and buffers of pH 1.2, pH 4.5, pH 6.8, pH 7.4 buffer and subjected to mechanical shaking at 200 rpm for 2 hrs. The resultant dispersions were collected and filtered through 0.2 µ filters and the concentration of drug was determined from absorbance at 290 nm. The solid dispersion ratio was optimized based on the solubility studies performed at various pH conditions

9.2.4. Solid state characterization by X-Ray Diffraction Studies (XRD):

Crystallinity of the samples was determined using the Bruker D8 Advance Analytical with copper target. Samples were properly ground and uniformly spread in the sample holders made of PMMA (8.5 mm, φ25mm, 1mm depth, airtight). The samples were loaded on to the diffractometer and scanned over a range of 2-Theta values from 3^0 to 45^0 at a scan rate of 0.1^0 /sec.

Powder XRD patterns of Fenofibrate, HPMC 3pcs, and optimized solid dispersion and stability sample exposed to 40^0C & 75% RH for 1 month were recorded using diffractograms (Bruker) and Cu-kα radiation.

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9.2.5. Investigation of chemical interaction between drug and carrier in solid dispersion by FTIR:

Studies of drug matrix interaction have a substantial impact on stability and solubility of solid dispersion. Hydrogen bonding between drug and carrier increases the stability of drug in the matrix. The interaction between drug and carrier in solid dispersion were studied by FTIR spectroscopy (Perkin Elmer FT-IR 410). FTIR was performed by KBr pellet method. Drug and KBr were taken in 1:100 ratio and ground in mortar for even distribution of sample and KBr. Then it was prepared in the form of disk by applying pressure of 5 tons for 5 min using a hydraulic press and subjected to IR. The software used was spectrum (version 6.1.0) in the wave number range of 400-4000 cm^{-1}. The resolution is 4 cm^{-1}.

9.3 STABILITY STUDIES OF SOLID DISPERISON

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light, and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions.

Table 25: Stability studies, storage conditions and duration of study

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	25ºC ± 2º C/60% RH ± 5% RH or 30ºC ± 2º C/65% RH ± 5% RH	12 months
Intermediate**	30ºC ± 2º C/65% RH ± 5% RH	6 months
Accelerated	40ºC ± 2º C/75% RH ± 5% RH	3 months

* It is up to the applicant to decide whether long term stability studies are preformed at 25ºC ± 2º C/60% RH ± 5% RH or 30ºC ± 2º C/65% RH ± 5% RH.

** If 30ºC ± 2º C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

Before subjecting to stability studies, solid dispersion samples were analyzed by DSC, FTIR and XRD studies and initial thermograms and spectra were recorded. Then samples were subjected to accelerated conditions, 40ºC ± 2º C/75% RH ± 5% RH. After 4 weeks, DSC thermograms, FTIR and XRD patterns of solid dispersion samples were recorded and compared with initial thermograms and spectra of respective samples.

9.4. PREFORMULATION STUDIES OF TABLET

Preformulation testing is an investigation of physical and chemical properties of a solid dispersion alone and when combined with excipients. It is the first development in the rationale development of the dosage forms.

Preformulation studies yield necessary knowledge to develop suitable formulation. It gives information needed to define the nature of the drug substance and provide a dosage form. Hence, the following pre-formulation studies were performed for the obtained sample of drug.

9.4.1. Physical characterization of solid dispersion.

The solid dispersion was characterized for its physical properties such as its appearance, density, flow properties, particle size distribution and solubility.

a).Particle size distribution:

Particle Size Determination (PSD) of blends of 12 formulations was determined by Retsch apparatus type AS 200.

9.4.2. Drug-Excipients compatibility studies:

A small amount of physical mixture of the solid dispersion and excipients was placed in a vial, and rubber stopper was placed on the vial and sealed properly. After storage for a period of 4 weeks at 40°C / 75% RH, the sample was observed physically for any changes by comparing with the initial physical mixture.

Table 26: Excipient Compatibility Studies

	Ingredients	Ratio	Code
1	Solid dispersion	--	A
2	Solid dispersions + Mannitol	1:1	B
3	Solid dispersions + Sorbitol	1:1	C
4	Solid dispersions + Lactose	1:1	D
5	Solid dispersions+ Polyplasdone xl	1:1	E
6	Solid dispersions + Mg Stearate	1:1	F

9.5. Formulation studies

9.5.1. Development Strategy:

Following ingredients were selected for formulation development of solid dispersion based on the literature search and preformulation studies.

Each Batch size: 150 Tablets.

Manufacturing Process:

1. Solid dispersion and Mannitol/ Lactose (low moldable saccharides) and polyplasdone were accurately weighed individually.
2. Solid dispersion and polymer and ppxl were then mixed well to form uniform blend.
3. The above blend was granulated using water/ ethanol as granulating fluid and sorbitol (High moldable saccharide) as the binding agent.
4. The granulated mass was then dried and milled using a quadraco mill 40G at speed 30 Hz.
5. Extragranular part (magnesium stearate) was weighed.

6. Step 5 part was added to the step 4 granules and mixed uniformly.

7. The blend was then compressed into tablets using suitable punch (10mm) and compression machine.

8. Tablets were subjected to various moisture conditions for moisture treatment to attain sufficient hardness and DT.

Formulation	**F1 (mg/tablet)**	**%w/w**	**F2 (mg/tablet)**	**%w/w**	**F3 (mg/tablet)**	**%w/w**
Solid dispersion	160		160		160	
Mannitol	166.5		166.5		-	
Lactose	-		-		166.5	
Sorbitol	18.5		18.5		18.5	
Polyplasdone XL	-		-			
Magnesium sterate	5		5		5	
Water	qs		-		-	
Ethanol	-		qs		qs	
Total Weight	350		350		350	

Table no. 27: Formulation F1 to F3

Formulation	F4 (mg/tablet)	%w/w	F5 (mg/tablet)	%w/w	F6 (mg/tablet)	%w/w
Solid dispersion	160		160		160	
Mannitol	162		157.5		153	
Lactose	-		-		-	
Sorbitol	18		17.5		17	
Polyplasdone XL	5		10		15	
Magnesium sterate	5		5		5	
Water	-		-		-	
Ethanol	qs		qs		qs	
Total Weight	350		350		350	

Table no. 28: Formulation F4 to F6

9.6 EVALUATION PARAMETERS

9.6.1 Blend Characterization

Blend Characterization parameters such as bulk density, tapped density, Compressibility Index, Hausner's ratio, Angle of Repose were performed and computed to 12 formulations of trial batches.

Particle Size Determination (PSD) of blends of 6 formulations was determined by Retsch apparatus type AS 200.

9.7 MOISTURE UPTAKE STUDIES OF THE TABLETS

Moisture treatment is the main step in the formulation of the tablets by WOWTAB technology

The tablets are compressed at a very low hardness of 1 to 2 KP. The mechanical strength of the tablets was substantially increased after moisture treatment and moisture treatment also has a negative influence on disintegration time which is of main role in orodispersible tablets.

Various super saturated salt solutions are used for attaining specific relative humidity values. Three different relative humidities have been selected to study the effect of moisture treatment on hardness and disintegration time of the tablet

SALT BATH	PUBLISHED RH AT 25°C
LITHIUM BROMIDE	6.37%
LITHIUM CHLORIDE	11.30%
POTASSIUM ACETATE	22.51%
MAGNESIUM CHLORIDE	32.80%
POTASSIUM CARBONATE	43.16%
MAGNESIUM NITRATE	52.89%
SODIUM BROMIDE	57.57%
POTASSIUM IODIDE	68.86%
SODIUM CHLORIDE	75.30%
POTASSIUM CHLORIDE	84.34%
POTASSIUM SULFATE	97.30%

*Based on: Humidity Fixed Points of Binary Saturated Aqueous Solutions

Table no. 29: salts for moisture treatment

9.7.1 Preparation of super saturated Magnesium chloride solution (33% RH)

Take 100ml of water and magnesium chloride is added to it slowly with stirring and the addition is continued until the liquid is completely saturated and excess amount of salt

added gets settled at the bottom of the container.

Care should be taken regarding the temperature of the solvent during addition of salt because high temperature may increase the solubility of the salt.

The super saturated solution was placed at the bottom of the dessicator and the chamber lid is tightly closed by applying wax at the brim so that the chamber retains the moisture.

9.7.2 Preparation of super saturated Magnesium nitrate solution (53%RH)

Take 100ml of water and magnesium nitrate is added to it slowly with stirring and the addition is continued until the liquid is completely saturated and excess amount of salt added gets settled at the bottom of the container.

Care should be taken regarding the temperature of the solvent during addition of salt because high temperature may increase the solubility of the salt.

The super saturated solution was placed at the bottom of the dessicator and the chamber lid is tightly closed by applying wax at the brim so that the chamber retains the moisture.

9.7.3 Preparation of super saturated potassium chloride solution (84%RH)

Take 100ml of water and magnesium chloride is added to it slowly with stirring and the addition is continued until the liquid is completely saturated and excess amount of salt added gets settled at the bottom of the container.

Care should be taken regarding the temperature of the solvent during addition of salt because high temperature may increase the solubility of the salt.

The super saturated solution was placed at the bottom of the dessicator and the chamber lid is tightly closed by applying wax at the brim so that the chamber retains the moisture.

9.8 MOISTURE TREATMENT

The tablets formulated at low hardness of 1 to 2 KP and the tablets are placed in the

dessicators containing the super saturated salt solutions and the lid is tightly closed and kept undisturbed for 36 to 48 hrs

Moisture treatment for few tablets was continued till 4 to 5 days to find the effect for prolonged moisture treatment.

Formulation will be optimized based on the hardness and the disintegration time before and after the moisture treatment

9.9 EVALUATION OF FAST DISINTEGRATING TABLETS (USP 29- NF 34)

All the batches of tablets were evaluated for various physical parameters like thickness, weight variation, friability, hardness, drug content and dissolution as per pharmacopoeial standards.

A) Thickness:

Thickness of tablet is important for uniformity of tablet size. Thickness of tablets can vary with no change in weight because of the difference in the density of the granulation and the pressure applied to the tablets, as well as the speed of the compression machine. Ten tablets were randomly selected and thickness was measured using vernier calipers and recorded.

B) Weight variation:

20 tablets were taken and weighed individually on a digital weighing balance. Average weight was calculated and the individual tablet weight was compared to the average. The tablet passes the U.S.P. test if no more that 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

$$\text{Average weight} = \frac{\text{Weight of 20 tablets}}{20}$$

Table 30: Acceptance criteria for tablet weight variation

Average weight of tablet(mg)	% difference allowed
130 or Less than	± 10

130-324	± 7.5
More than 324	± 5

C) Crushing strength:

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shakes of handling in manufacture, packaging and shipping. Hardness generally measures the tablet crushing strength. Changes in hardness results in differences in disintegration and dissolution characteristics. The crushing strength of the tablet was determined using Schleuniger hardness tester.

D) Friability test:

Ten tablets from each batch were examined for friability using Roche Friabilator and the equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated. Tablet that loose less than 0.5- 1 % of the tablet weight were considered acceptable.

%Friability = (Loss in weight / Initial weight) x 100

E) Content uniformity test:

Ten tablets from each formulation were powdered. The powdered sample equivalent to 100 mg of drug was transferred to a volumetric flask and dissolved in methanol, mixed and filtered. Required amount of phosphate buffer pH 7.4 was added to the filtrate, suitably diluted with media and drug content was analyzed against blank by UV spectrophotometer at 331 nm. The percentage of drug present in the tablets was calculated.

G) Disintegration test

The time for disintegration of ODTs is generally less than one minute and actual disintegration time that patient can experience ranges from 5-30 seconds. The standard procedure of performing disintegration test for these dosage forms has several limitations and they are not suitable for the measurement of very short disintegration times. The method needs to be modified for ODTs as disintegration is required without water; thus the test should mimic disintegration in salivary contents. A modified dissolution apparatus is applied to an ODT with a disintegration time that is too fast to distinguish differences between tablets when the compendial method is used. A basket sinker containing the tablets is placed just below the water surface in a container with 900 mL of water at 37 ^{0}C, and a paddle rotating at

100 rpm is used. The disintegration time is determined when the tablet has completely disintegrated and passed through the screen of the sinker

H) In vitro dissolution studies:

Dissolution study was conducted for optimized formulation using USP type-II apparatus (ELECTROLAB). The dissolution test was performed in buffers of different pH and in water containing 0.5% sodium lauryl sulphate as the dissolution medium at 75 rpm and at a temperature of 37 ^{0}C ± 0.5 ^{0}C for one hour. Five milliliters of aliquots were periodically withdrawn at time intervals of 2, 5, 10, 20, 30, 45, and 60 minutes and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were diluted and analyzed spectrophotometrically at 290nm.

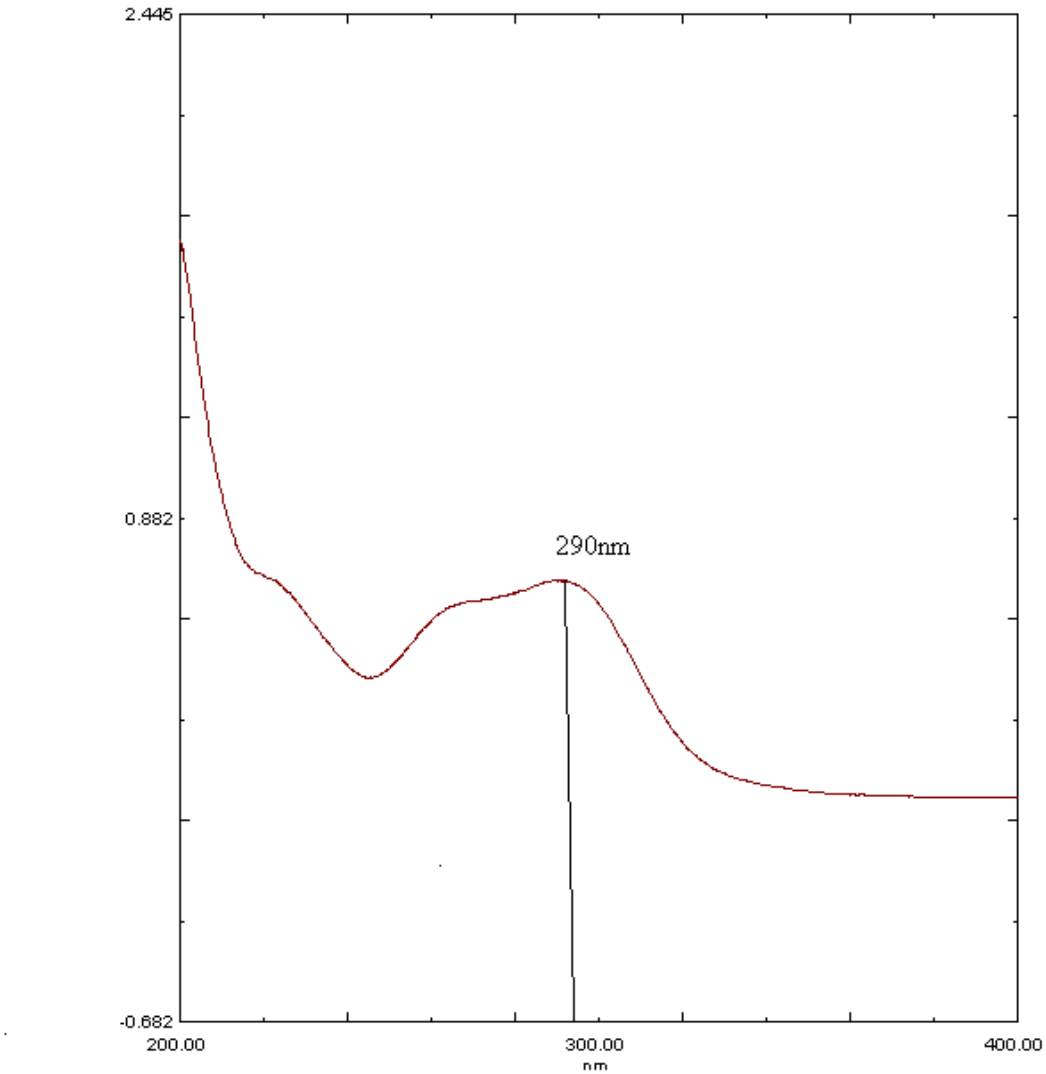
9.9.3. Accelerated Stability study of the optimized batch

In order to determine the change in evaluation parameters and in vitro release profile on storage, stability study of optimized batch was carried out at accelerated storage condition at temperature 40° ± 2° C and 75% ± 5% RH in a humidity chamber for 1 month. Sample were withdrawn after 30 days interval and evaluated for change in physical appearance .

X. RESULTS AND DISCUSSION.

10.1 Drug Analysis:

10.1.1. Determination of λmax



No.	P/V	Wavelength nm.	Abs.
1		290.80	0.689
2		245.20	0.385

Figure 8: Spectrum of Fenofibrate

10.1.2. Procedure for Calibration curve

Calibration Curve of Fenofibrate in water

S.No	Concentration in mcg/ml	Absorbance at 290.0nm
1	0	0
2	2	0.129
3	4	0.243
4	6	0.362
5	8	0.486
6	10	0.592
7	12	0.729

Table no. 31: calibration curve of Fenofibrate

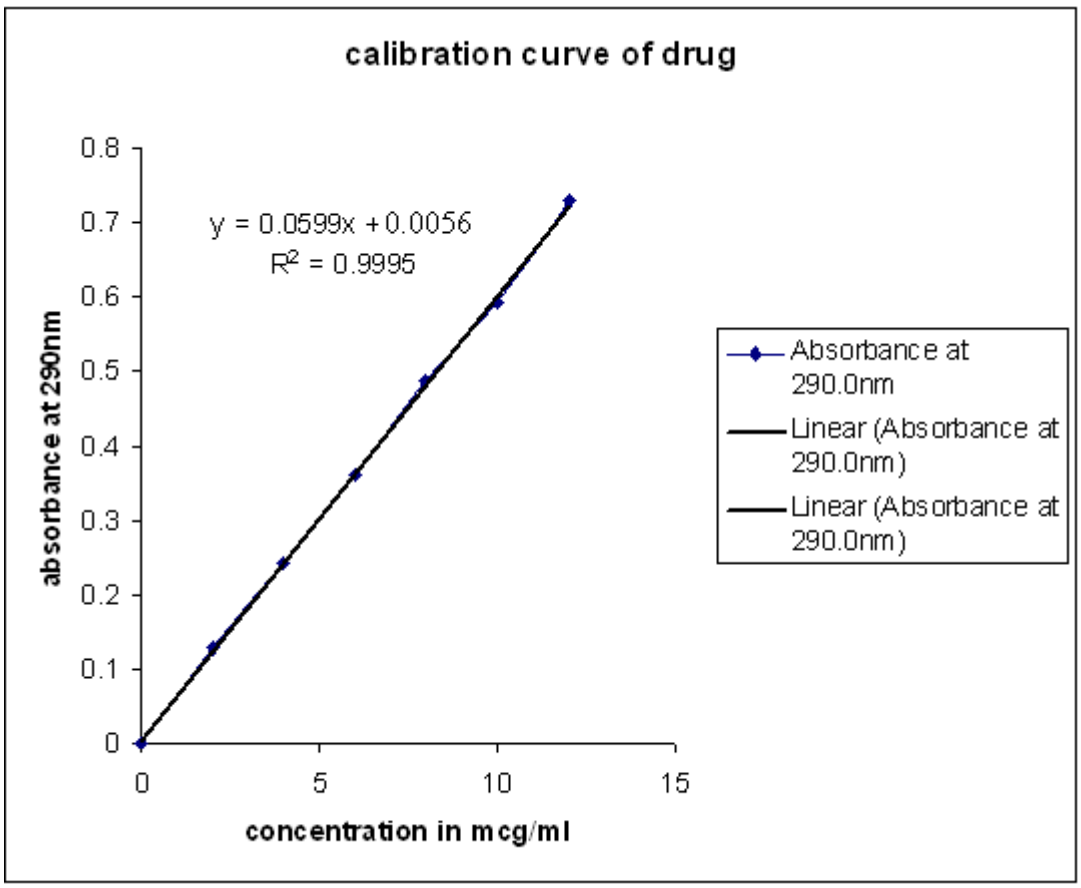


Figure no: 9 calibration curve of Fenofibrate

Inference: The λ_{max} of Fenofibrate was found to be 290 nm**.** The linear equation was A=0.0593 x concentration (mcg/mL) +0.0056 Different standard concentrations and their

absorbance values were shown in the table 23. Goodness of fit of regression equation was supported by regression value of 0.9995 indicating linearity in the absorbance with increase in concentration.

10.1.3. Particle size determination:

Dry sieve analysis for particle size determination

Table 32: Particle size determination of Fenofibrate

Sieve Mesh Number	Sieve Size Opening(µm)	Mass of Sample Retained on Each Sieve(g)	Percentage of Sample Retained on Each Sieve (%)	Cumulative Percentage of Sample Retained on Each Sieve (%)
20	841	0.17	3.4	3.4
40	420	0.02	0.4	3.8
60	250	0.11	2.2	6
80	177	0.36	7.3	13.3
100	149	0.26	5.2	18.5
120	125	0.24	4.8	23.3
Pan	-	3.76	76.4	99.7

Inference: From the particle size distribution data, it was observed that, 99.7 % of API particles were found to be below of 12 microns in size.

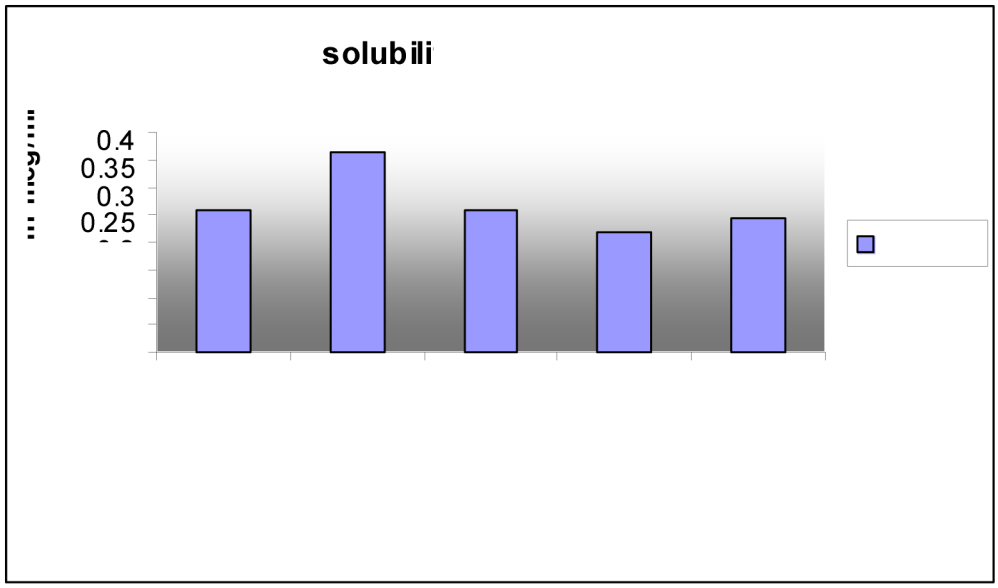
10.1.4. Solubility studies:

Solubility of drug in different buffers:

Table 33: Solubility data of pure drug

Medium	Solubility(µg/ml)
Water	0.2568
0.1N HCl	0.3637
pH4.5 Acetate buffer	0.2568
pH6.8 Phosphate buffer	0.2184
pH7.4 Phosphate buffer	0.2426

Figure 10: pH Solubility plot of pure drug



Inference: Solubility studies of pure drug were performed and studies showed that drug is showing very poor solubility in all the medias. Solubility of drug in different pH conditions was less than 0.4mcg/ml and the solubility of the drug is not influenced by the changes in the pH of the media

The uniform solubility pattern of fenofibrate in all the medias was attributed to the lack of chemically ionisable groups in the structure.

10.1.5 DSC thermogram of Fenofibrate

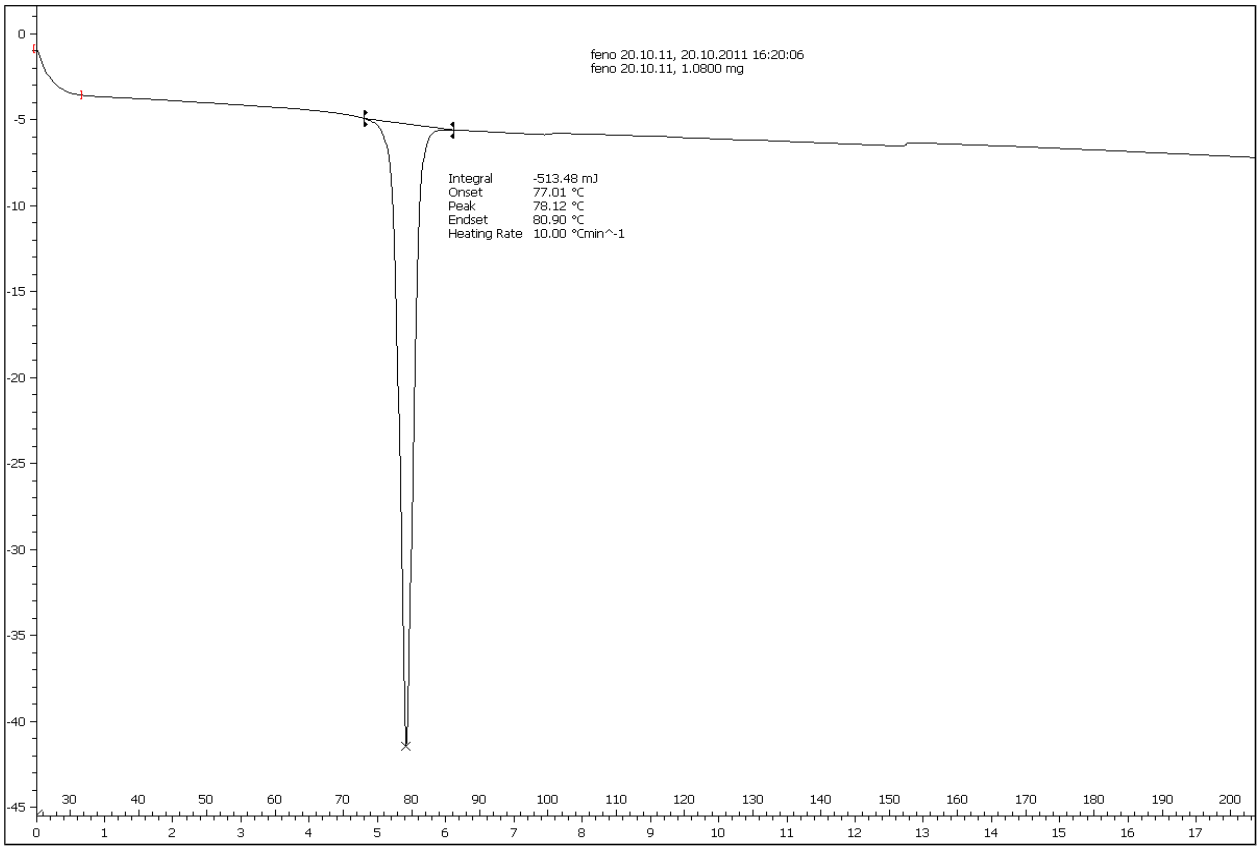


Figure 11: Thermogram of API

Inference: Polymorphic studies were performed by DSC for API. The melting range of API was found to be 78 to 82 º C. The sharp peak in the thermogram of API indicates crystalline nature of drug.

10.1.6. X-Ray Diffraction study of Fenofibrate

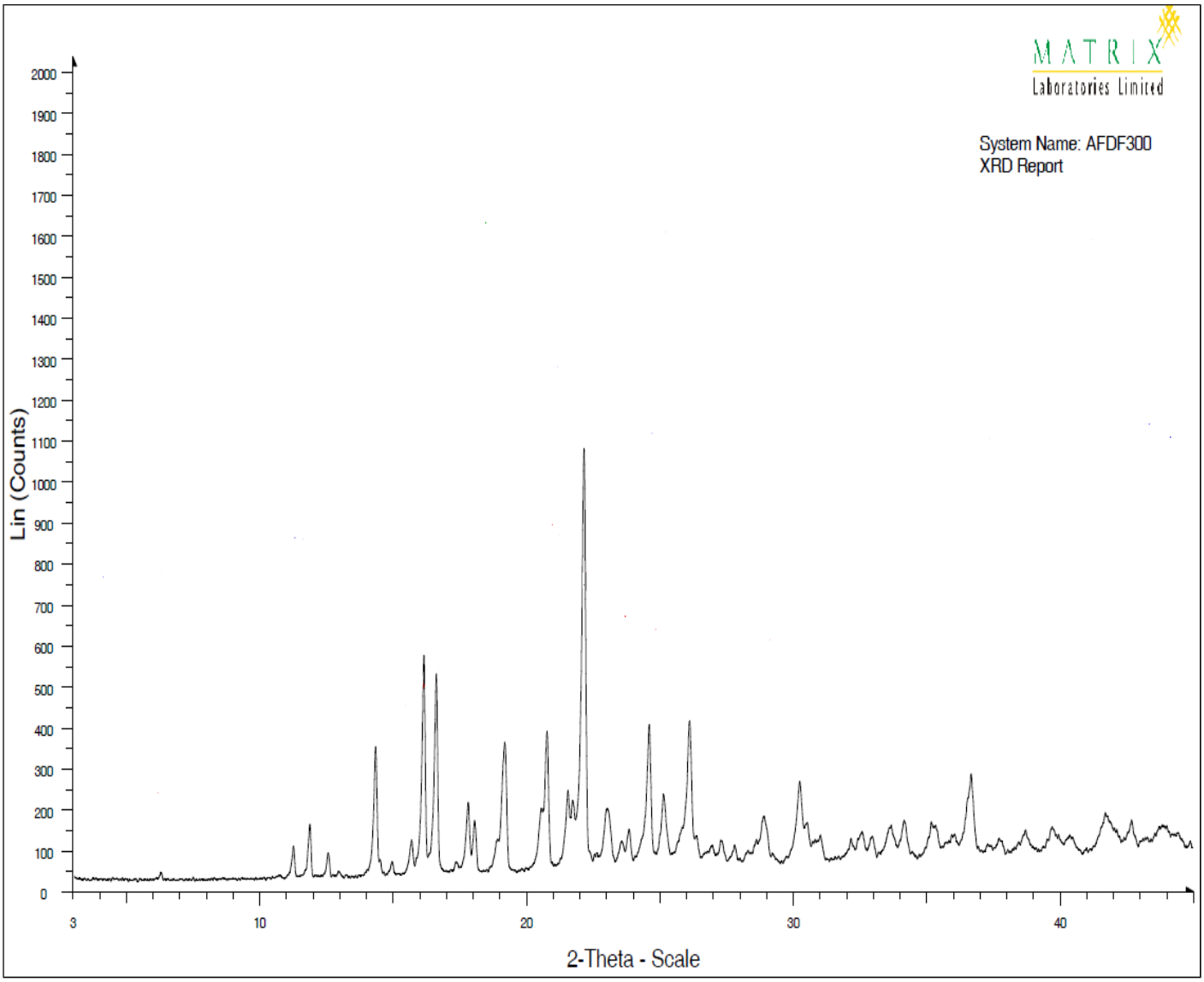


Figure 12: X RAY DIFFRACTION PATTERN OF FENOFIBRATE

Inference: The X-ray diffractogram of Fenofibrate has sharp peaks at diffraction angles (2θ) 6.689°, 11.482°, 12.707°, 13.352°, 16.898°, 18.078°, 19.054°, 20.059°, 20.400°, 22.386°, 23.110°, 23.789°, 24.03°, 25.353°, 26.835°, 27.417°, 27.864°, 28.454°, 29.337°, 29.904°,31.416°,32.471°,33.261°,33.713°,34.162°,34.891°,35.339°,36.563°,37.236°,38.302°, 40.710° showing a typical crystalline pattern.

10.1.7. Fourier Transform Infra Red spectrum of Fenofibrate

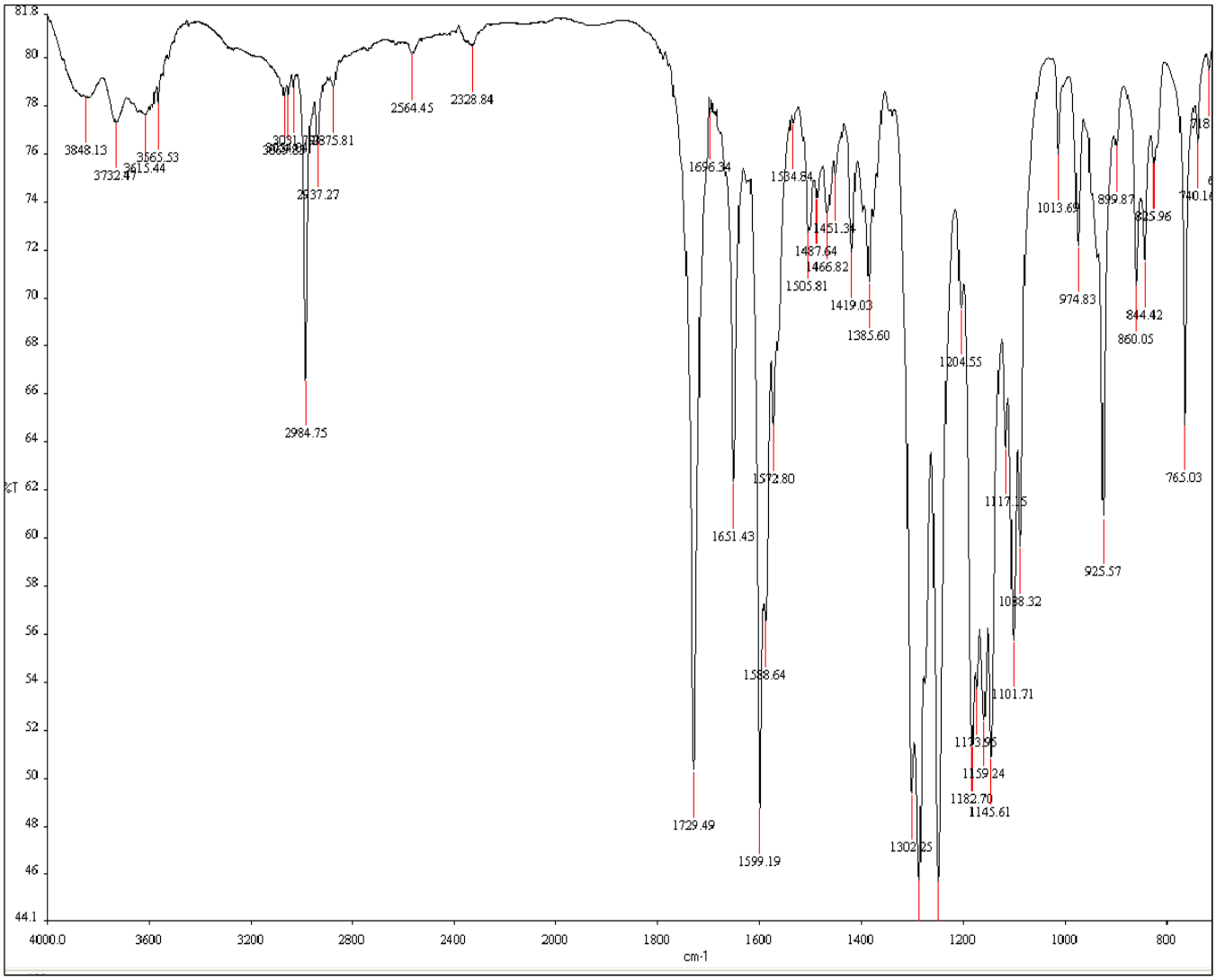


Figure 13: FTIR Spectrum of Fenofibrate

Inference: Characteristic peaks of Fenofibrate were observed from FTIR peaks and summarized in Table 13.

Table 34: FTIR peaks and their functional groups of Fenofibrate

Functional Group	IR range (cm^{-1})	Peak observed (cm^{-1})

Usually O-H carboxylic	3800-3550	3842.12
		3782.30
O-H alcoholic	3500-3100	3562
= C-H & = CH_2	3020-3100	3031.02
CH_3, CH_2 & CH	2850-3000	2990.06
		2929.52
		2865.20
C-H	2690-2840	2736.39
C=O (saturated aldehyde)	1720-1740	1729.35
C=O (saturated ketone)	1710-1720	1712.53
		1710.58
CH_2 & CH_3	1350-1470	1599.30
		1442.98
OH bending	1330-1430	1385.66
		1370.31
		1359.87
		1331.01
C=O	1210-1320	1299.75
		1262.05
O-H bonded	970-1250	1245.93
		1223.87
C-N	1000-1250	1167.89
O-H bonded	970-1250	1155.96
		1126.53
		1117.16
		1104.27
		1074.96
		1055.16
		1044.76
		1013.75
=C-H & = CH_2	880-995	991.61
		969.25
		925.04
= CH_2	780-850	842.41
		765.58

10.1.8. Powder and Flow Properties of API

Table 35: Flow and powder properties of API

Parameters	API
Bulk density (gm/ml)	0.208
Tapped density (gm/ml)	0.333
Compressibility Index (CI) %	37.53
Hausner's ratio (HR)	1.51
Angle of repose (θ)	45

Inference: Flow and powder properties of API were very very poor and may hang up hence tablets can be prepared by granulation method.

10.1.9. Drug content estimation

Table 36: Drug content in solid dispersions

Formulation code	% drug content
Drug	99.86
SD1	98.65
SD2	99.12
SD3	98.01
SD4	98.35
SD5	99.7
SD6	98.5
SD7	99.36
SD8	99.13
SD9	97.89
SD10	99.3
SD11	99.54
SD12	98.63
SD13	99.42
SD14	99.26
SD15	98.92
SD16	98.79
SD17	98.35
SD18	99.6
SD19	99.1
SD20	98.7
SD21	97.8
SD22	99.2
SD23	98.6
SD24	98.1
SD25	99.4

Inference: % drug content in Solid dispersions was found and it is above 97 for all solid dispersions.

10.1.1. Solid state characterization of solid dispersion by Differential Scanning Calorimetry (DSC)

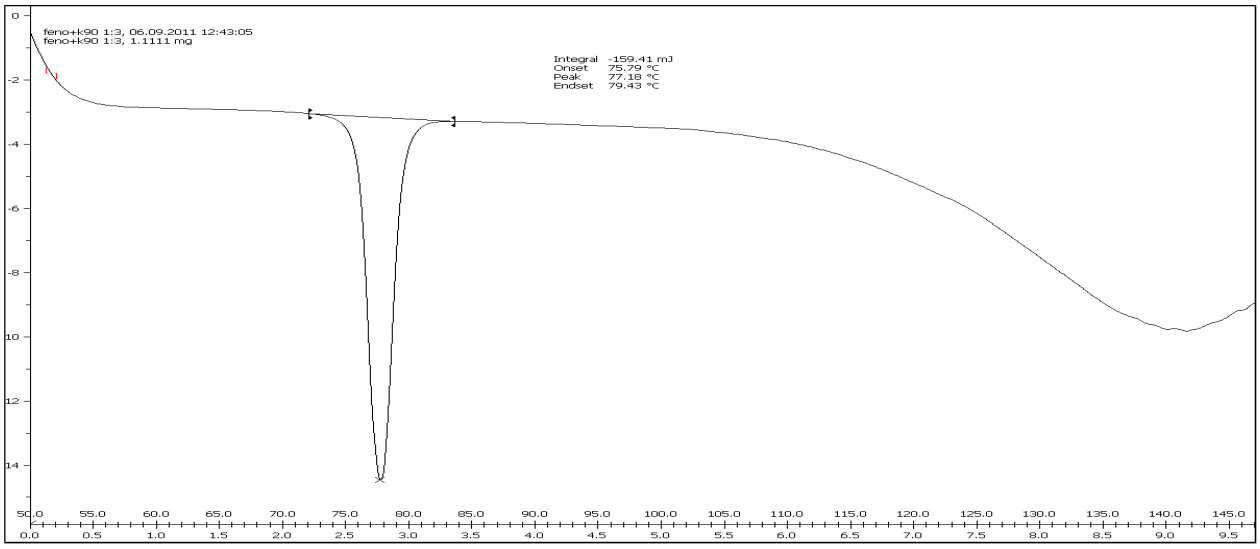


Figure no: 14 DSC THERMOGRAM OF SD 1 (FENOFIBRATE+PVP K90)

Inference: DSC thermogram of solid dispersion of drug and PVP K90 showing a sharp peak obtained at 77.08^0c. This peak indicates the crystalline form of the drug in the dispersion as the peak is obtained in the melting point range of the drug.

There was no change in the polymorphic form of the drug from crystalline form to amorphous form. Hence the solid dispersion has not been formed

Hence this formulation cannot be considered for further studies of solubility.

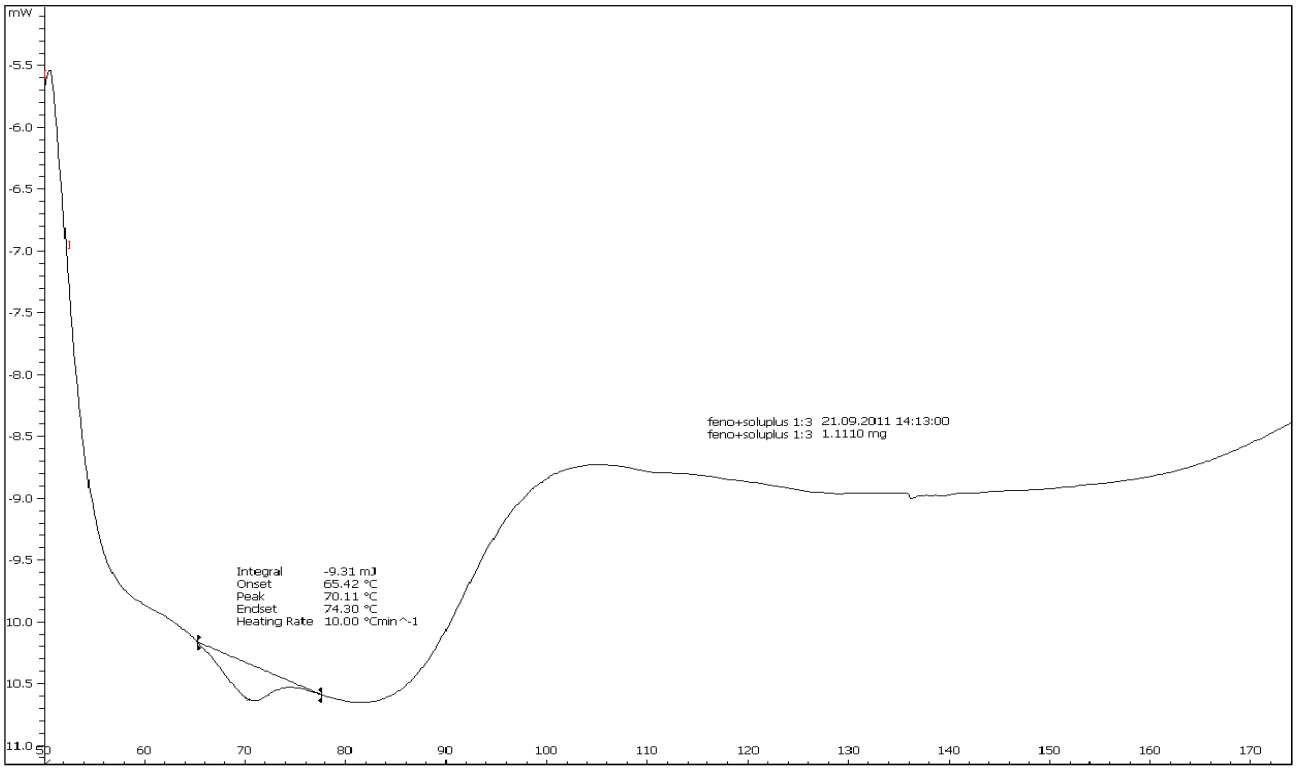


Figure no: 15 DSC THERMOGRAM OF SD 2 (FENOFIBRATE + SOLUPLUS)

Inference:

Dsc thermogram of solid dispersion of drug and soluplus does not show any sharp peak in the melting point range of the drug (78 to 82^0c).

This indicates that the drug molecular form has been changed from crystalline form to amorphous form and dispersion is formed between the drug and the polymer.

Hence this solid dispersion can be chosen for the further solubility studies and characterization through x ray diffraction and other studies.

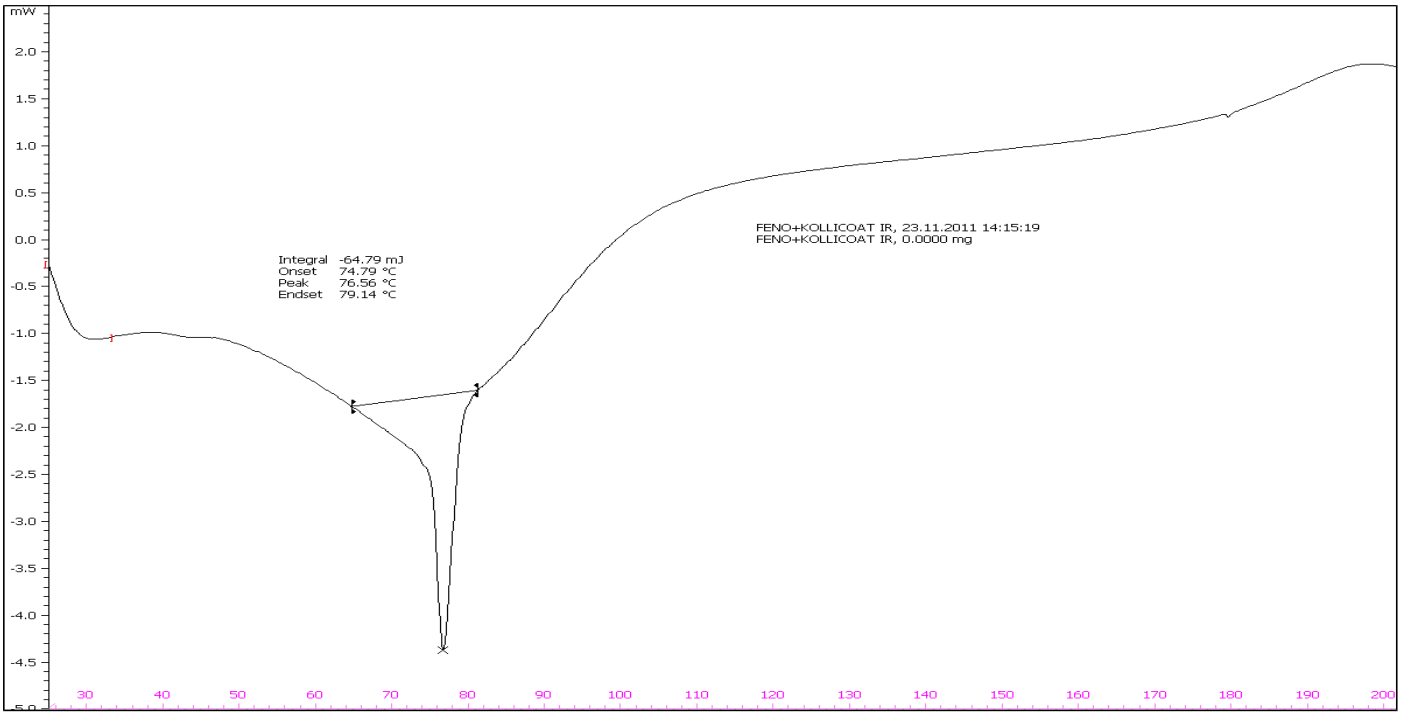


Figure no: 16 DSC THERMOGRAM OF SD 3 (FENOFIBRATE + KOLLICOAT IR)

Inference:

Dsc thermogram of solid dispersion of drug and kollicoat IR showing a sharp peak obtained at 77^0c. This peak indicates the crystalline form of the drug in the dispersion as the peak is obtained in the melting point range of the drug.

There was no change in the polymorphic form of the drug from crystalline form to amorphous form. Hence the solid dispersion has not been formed

Hence this formulation cannot be considered for further studies of solubility.

The appearance of the drug peak indicates a poor molecular interaction between the drug and the polymer

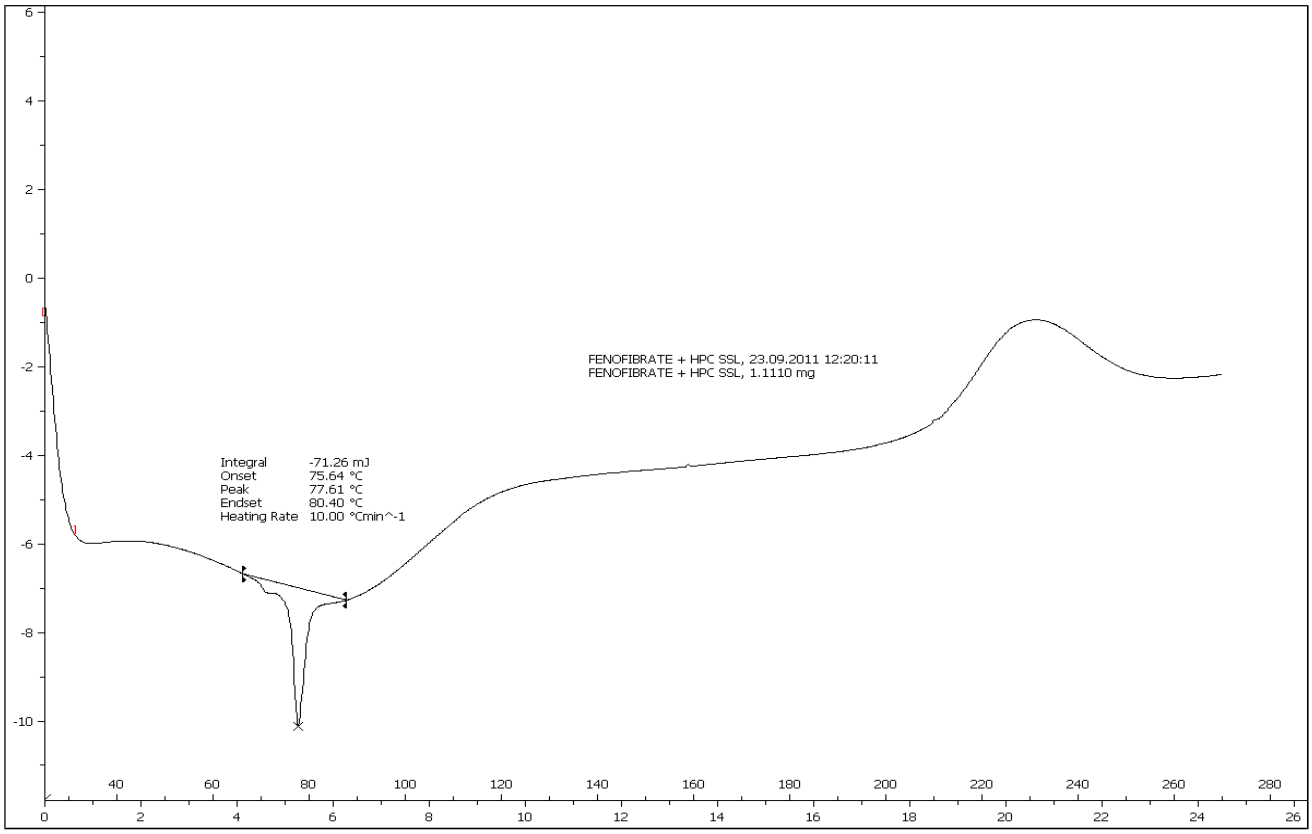


Figure no: 17 DSC THERMOGRAM OF SD 4 (FENOFIBRATE + HPC SSL)

Inference:

DSC thermogram of solid dispersion of drug and HPC SSL showing a sharp peak obtained at 77.61^0c. This peak indicates the crystalline form of the drug in the dispersion as the peak is obtained in the melting point range of the drug.

There was no change in the polymorphic form of the drug from crystalline form to amorphous form. Hence the solid dispersion has not been formed

Hence this formulation cannot be considered for further studies of solubility.

The appearance of the drug peak indicates a poor molecular interaction between the drug and the polymer

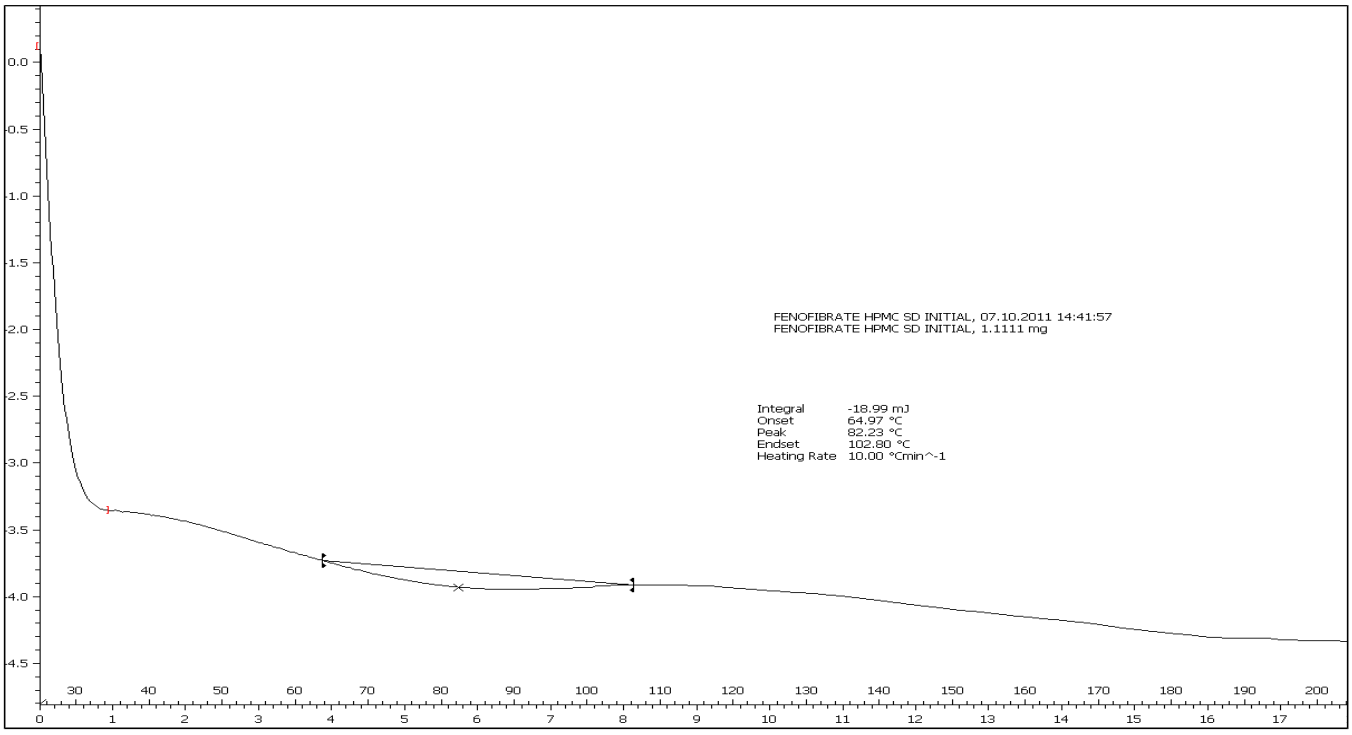


Figure no: 18 DSC THERMOGRAM OF SD 5 (FENOFIBRATE + HPMC 3CPS)

Inference: DSC thermogram of solid dispersion of drug and soluplus does not show any sharp peak in the melting point range of the drug (78 to 82^0c).

This indicates that the drug molecular form has been changed from crystalline form to amorphous form and dispersion is formed between the drug and the polymer.

Hence this solid dispersion can be chosen for the further solubility studies and characterization through x ray diffraction and other studies

Conclusion of DSC studies of solid dispersions SD 1 to SD 5:

From the differential scanning calorimetry studies of the 5 solid dispersions it was concluded that the solid dispersions SD 2(drug + soluplus) and SD 5(drug + hpmc 3cps) has shown a change in the polymorphic form of the drug from crystalline to amorphous form.

Hence these two formulations have been chosen for the solubility studies to optimize the ratio of drug and the polymer

10.2. Solubility studies

Table no: 37 Solubility studies of solid dispersions SD 6 to SD 15 (fenofibrate + soluplus) in water

Solid dispersion	Drug : carrier ratio				
	1:0.5	1:1	1:2	1:3	1:4
Solvent evaporation method	9.28 µg/ml	29.06 µg/ml	81.02 µg/ml	83.25 µg/ml	88.30 µg/ml
Melt fusion method	5.40 µg/ml	18.01 µg/ml	69.08 µg/ml	75.60 µg/ml	81.07 µg/ml

Table no: 38 Solubility studies of solid dispersions (fenofibrate + soluplus) in pH 1.2 buffer

Solid dispersion	Drug : carrier ratio				
	1:0.5	1:1	1:2	1:3	1:4
Solvent evaporation method	12.5 µg/ml	19.6 µg/ml	51.25 µg/ml	71.40.µg/ml	81.07 µg/ml
Melt fusion method	4.80 µg/ml	11.1 µg/ml	18.15 µg/ml	33.50 µg/ml	59.82 µg/ml

Table no: 39 Solubility studies of solid dispersions (fenofibrate + soluplus) in pH 4.5 acetate buffer

Solid dispersion	Drug : carrier ratio				
	1:0.5	1:1	1:2	1:3	1:4
Solvent evaporation method	14.46 µg/ml	42.14 µg/ml	62.67 µg/ml	108.21µg/ml	122.5 µg/ml
Melt fusion method	9.48 µg/ml	31.1 µg/ml	50.78 µg/ml	81.54 µg/ml	93.57 µg/ml

Table no: 40 Solubility studies of solid dispersions (fenofibrate + soluplus) in pH 6.8 phosphate buffer

Solid dispersion	Drug : carrier ratio				
	1:0.5	1:1	1:2	1:3	1:4

Solvent evaporation method	8.75 µg/ml	25.3 µg/ml	60 µg/ml	85.8 µg/ml	88.57 µg/ml
Melt fusion method	6.24 µg/ml	16.42 µg/ml	52.2 µg/ml	78.62 µg/ml	83.75 µg/ml

Inference: Comparative study between the solubility of solid dispersion formulated by solvent evaporation and melt fusion method is done to optimize the method of preparation of solid dispersion having maximum solubility

Solubility studies of SD 6 to SD15 in 5 different ratios 1:0.5, 1:1, 1:2, 1:3, 1:4 have been performed for both solvent evaporation and fusion method of preparation in all the medias water, pH 1.2 buffer, pH 4.5 acetate buffer, pH 6.8 phosphate buffer.

In all the pH conditions solid dispersion prepared by solvent evaporation method has shown better solubility compared to solid dispersion prepared by fusion method.

Solubility of the drug has been enhanced from 0.4 µg/ml to a maximum of 122.5 µg/ml in 4.5 acetate buffer showing a considerable increase in the solubility of the drug in the solid dispersion compared to the pure drug.

Table no: 41 Comparision of solubility profile of 1:4 ratio in all pH conditions:

Drug + soluplus 1:4	**water**	**1.2**	**4.5**	**6.8**
Solvent evaporation	88.30 µg/ml	81.07 µg/ml	122.5 µg/ml	88.57 µg/ml
Melt fusion	81.07 µg/ml	51.82 µg/ml	93.57 µg/ml	83.75 µg/ml

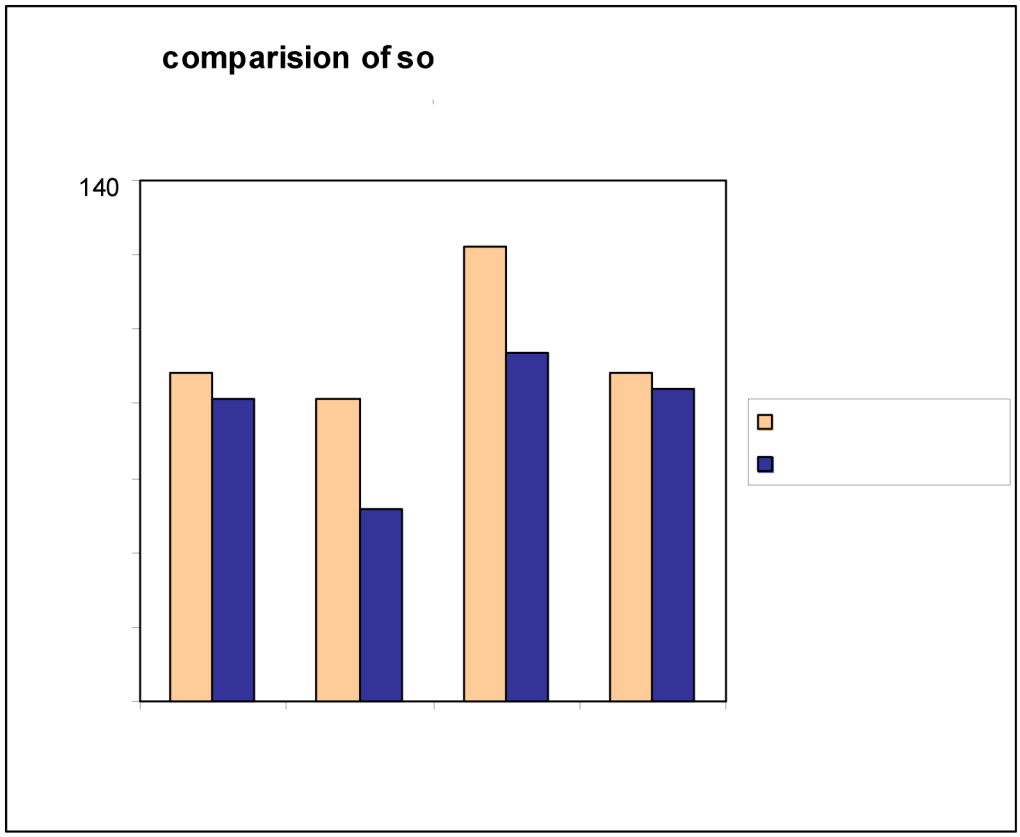


Figure no: 19: comparative solubility data of drug + soluplus

Solvent evaporation method can been preferred for the preparation of solid dispersion using soluplus as it is showing better solubility compared to the solid dispersion prepared by fusion method.

It can also be noted that there is a change in the solubility of the drug in the solid dispersion with the change in the pH of the media but solubility of the pure is not influenced by the change in the pH of the media because of the lack of ionisable groups in the structure.

10.2.1. Solubility studies of SD 16 to 25:

Table no: 42 Solubility studies of solid dispersions (fenofibrate + HPMC 3cps) in water

Solid dispersion	Drug : carrier ratio				
	1:0.5	1:1	1:2	1:3	1:4
Solvent evaporation method	3.92 µg/ml	4.25 µg/ml	6.07 µg/ml	18.75 µg/ml	19.98 µg/ml
Melt fusion method	6.23 µg/ml	8.54 µg/ml	11.21 µg/ml	25.53 µg/ml	31.6 µg/ml

Table no: 43 Solubility studies of solid dispersions (fenofibrate + HPMC 3cps) in pH 1.2 buffer

Solid dispersion	Drug : carrier ratio				
	1:0.5	1:1	1:2	1:3	1:4
Solvent evaporation method	0.714 µg/ml	3.57 µg/ml	6.07 µg/ml	9.28 µg/ml	11.42µg/ml
Melt fusion method	2.58 µg/ml	6.12 µg/ml	8.06 µg/ml	14.1 µg/ml	21.96 µg/ml

Table no: 44 Solubility studies of solid dispersions (fenofibrate + HPMC 3cps) in pH 4.5 acetate buffer

Solid dispersion	Drug : carrier ratio				
	1:0.5	1:1	1:2	1:3	1:4
Solvent	4.28 µg/ml	5.71 µg/ml	8.03 µg/ml	8.57 µg/ml	11.6 µg/ml

evaporation method					
Melt fusion method	9.54 µg/ml	11.11 µg/ml	13.24 µg/ml	19.28 µg/ml	30.8 µg/ml

Table no: 45 Solubility studies of solid dispersions (fenofibrate + HPMC 3cps) in pH 6.8 phosphate buffer

Solid dispersion	**Drug : carrier ratio**				
	1:0.5	**1:1**	**1:2**	**1:3**	**1:4**
Solvent evaporation method	1.78 µg/ml	3.57 µg/ml	7.35 µg/ml	9.82 µg/ml	14.1 µg/ml
Melt fusion method	9.51 µg/ml	14.22 µg/ml	19.67 µg/ml	25.89 µg/ml	40.89 µg/ml

Table no: 46 Solubility studies of solid dispersions (fenofibrate + HPMC 3cps) in pH 7.4 buffer

Solid dispersion	**Drug : carrier ratio**				
	1:0.5	**1:1**	**1:2**	**1:3**	**1:4**
Solvent evaporation method	3.57 µg/ml	3.75 µg/ml	4.821 µg/ml	10.89 µg/ml	12.32 µg/ml
Melt fusion method	7.54 µg/ml	11.61 µg/ml	18.14 µg/ml	26 µg/ml	39.28 µg/ml

Inference: Comparative study between the solubility of solid dispersion formulated by solvent evaporation and melt fusion method is done to optimize the method of preparation of solid dispersion having maximum solubility

Solubility studies of SD 16 to SD 25 in 5 different ratios 1:0.5, 1:1, 1:2, 1:3, 1:4 have been performed for both solvent evaporation and fusion method of preparation in all the medias water, pH 1.2 buffer, pH 4.5 acetate buffer, pH 6.8 phosphate buffer.

In all the pH conditions solid dispersion prepared by melt fusion method has shown better solubility compared to solid dispersion prepared by solvent evaporation method.

Solubility of the drug has been enhanced from 0.4 µg/ml to a maximum of 40.89 µg/ml in pH 6.8 phosphate buffer showing a considerable increase in the solubility of the drug in the solid dispersion compared to the pure drug.

Table no: 47 Comparision of solubility profile of 1:4 ratio in all pH conditions:

Drug + HPMC 1:4	**Water**	**1.2**	**4.5**	**6.8**	**7.4**
Solvent evaporation	19.98	11.42	11.6	14.1	12.32
Melt fusion	31.6	21.96	30.8	40.89	39.28

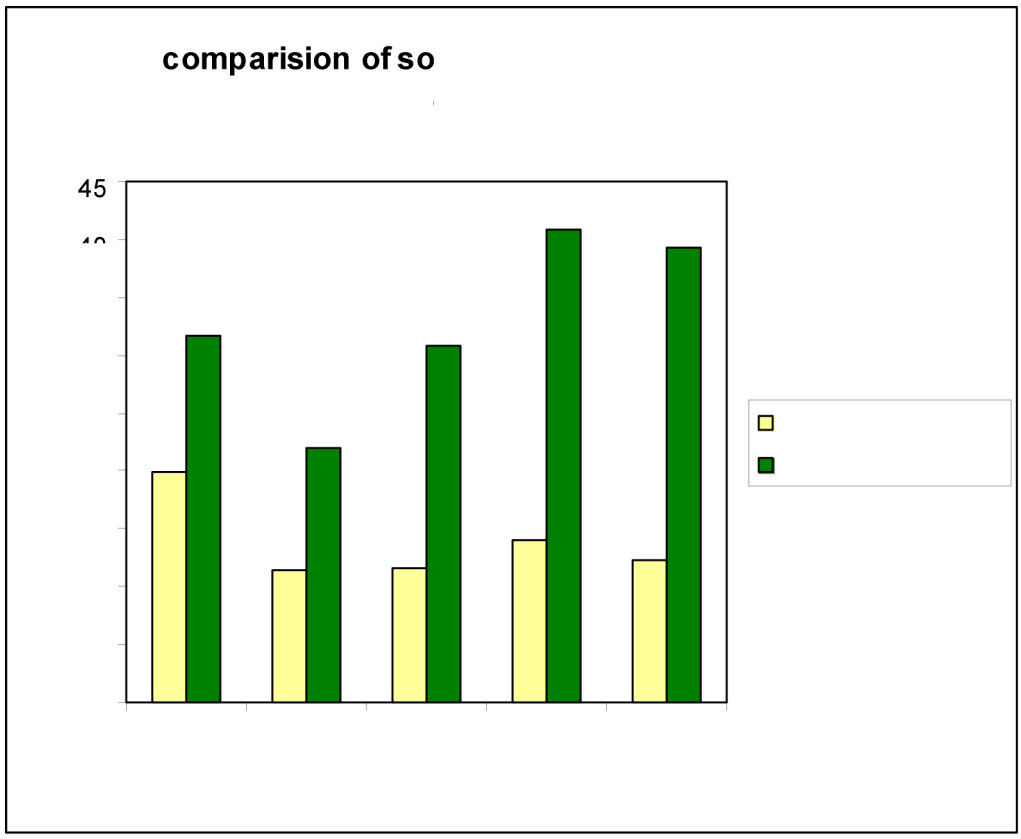


Figure no: 20 comparative solubility data of drug + HPMC

Melt fusion method can been preferred for the preparation of solid dispersion using HPMC 3cps as it is showing better solubility compared to the solid dispersion prepared by Solvent evaporation method.

It can also be noted that there is a change in the solubility of the drug in the solid dispersion with the change in the pH of the media but solubility of the pure is not influenced by the change in the pH of the media because of the lack of ionisable groups in the structure.

Conclusion of solubility studies of solid dispersions:

From the solubility studies it can be concluded that the SD 10 (drug + soluplus) has shown better solubility by solvent evaporation method than the melt fusion method because in the fusion method the melting range of drug is 78 to 82 ^{0}c and the glass transition temperature of the soluplus is 70oc. Hence polymer changes its form before the drug gets melted.

Because of formation of sticky mass there was no proper mixing of drug and polymer and hence the drug molecules can be seen as molecular lumps in the polymer

The drug has not got completely dispersed in the polymer.

In case of SD 25(drug + HPMC 3cps) solid dispersion prepared by melt fusion method has shown better solubility in all the pH conditions because the melting point of polymer is high compared to the drug and the glass transition temperature (Tg)of polymer is 170 to 180 ^{o}c.

Hence drug gets melted first and can be uniformly dispersed in the polymer and hence better stability can also be achieved by melt fusion method.

On the other hand in solvent evaporation method HPMC forms a viscous solution in the solvent and hence the drug may not get properly dispersed in the polymer during mixing and during evaporation there is an improper molecular interaction between the drug and the polymer.

The solid dispersion ratio of 1:4 has shown better solubility in all the formulations and this ratio is chosen for the optimized formula.

The optimized formula of 1:4 ratio of drug and soluplus prepared by solvent evaporation method and 1:4 ratio of drug and HPMC 3cps prepared by melt fusion method, have been loaded in the stability chamber (40 ^{o}c / 75% RH) for the stability study of the solid dispersion.

10.3 STABILITY STUDIES

10.3.1 Characterization of SD 10 and SD 25 by Differential scanning calorimetry (DSC)

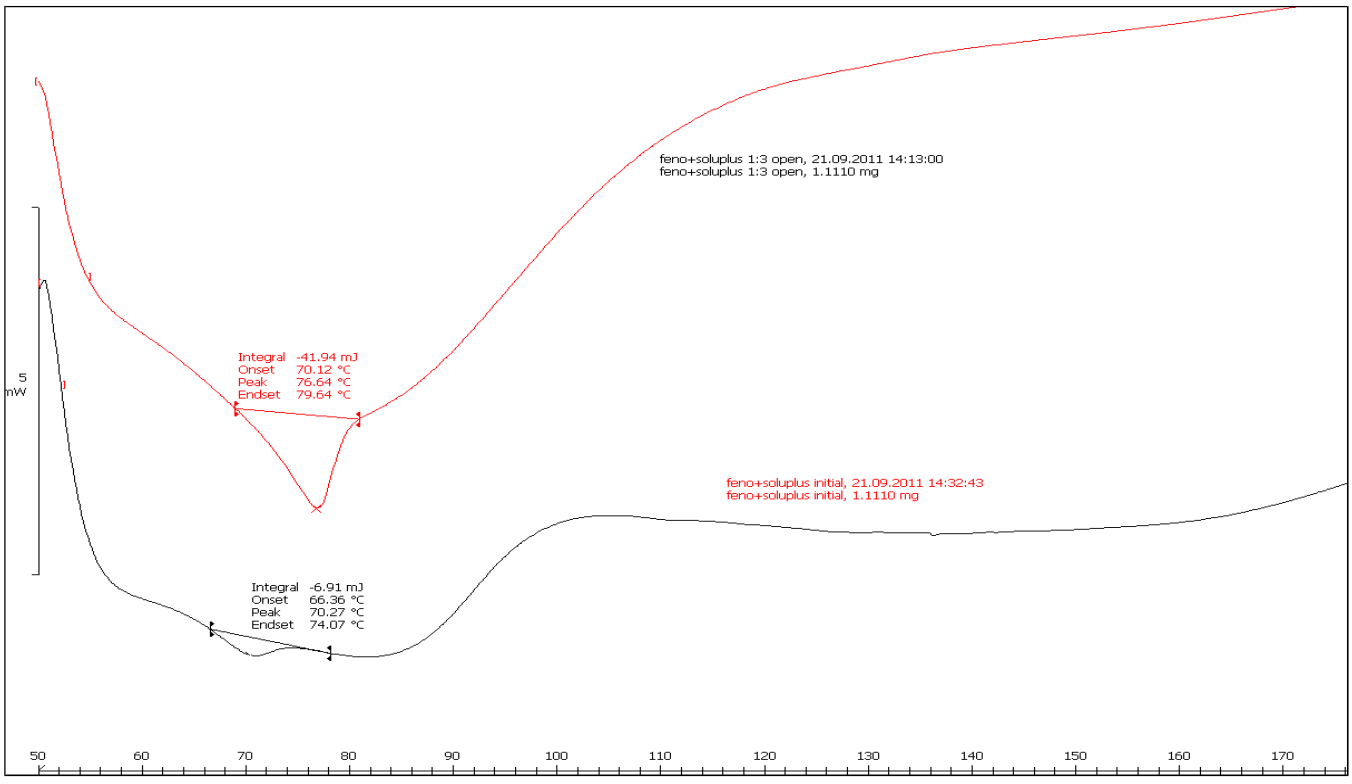


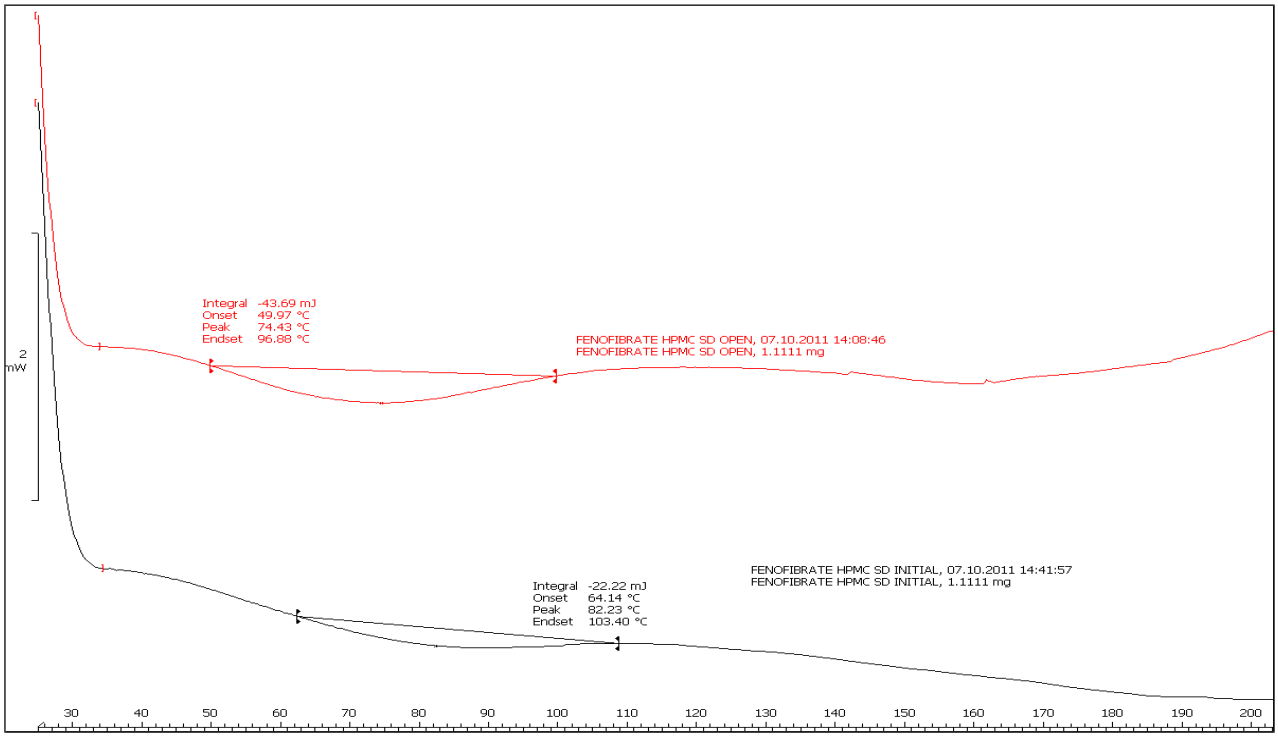
Figure no: 21 Comparison of DSC thermogram of initial and stability sample of solid dispersion 10 (Fenofibrate + soluplus)

Inference: After stability loading for one month at 40 °c / 75% RH the DSC thermogram of SD 10 (drug + soluplus) is showing the drug peak at 77 °c where as initial solid dispersion has not shown any sharp peak.

It indicates that the drug is re crystallizing from the solid dispersion after exposing to stability conditions.

Hence formulation is not considered for the further studies due to lack of stability

Figure no: 22 Comparision of DSC thermogram of initial and stability sample of solid dispersion 25 (fenofibrate + HPMC 3cps)



Inference: After stability loading for one month at 40 °c / 75% RH the DSC thermogram of SD 25 (drug + HPMC 3cps) is not showing any sharp peak and the DSC thermogram is similar to the initial thermogram of the solid dispersion

It indicates that the drug remained in the amorphous even after exposing to high temperature and moisture.

Hence this formulation (SD 25) can be considered as optimized formulation because of high stability can be used for further formulations instead of drug because of better solubility than the drug and it can be further characterized by XRD and FT IR studies for confirming the stability of the formulation.

10.3.2. Solid state characterization by X-Ray Diffraction Studies (XRD):

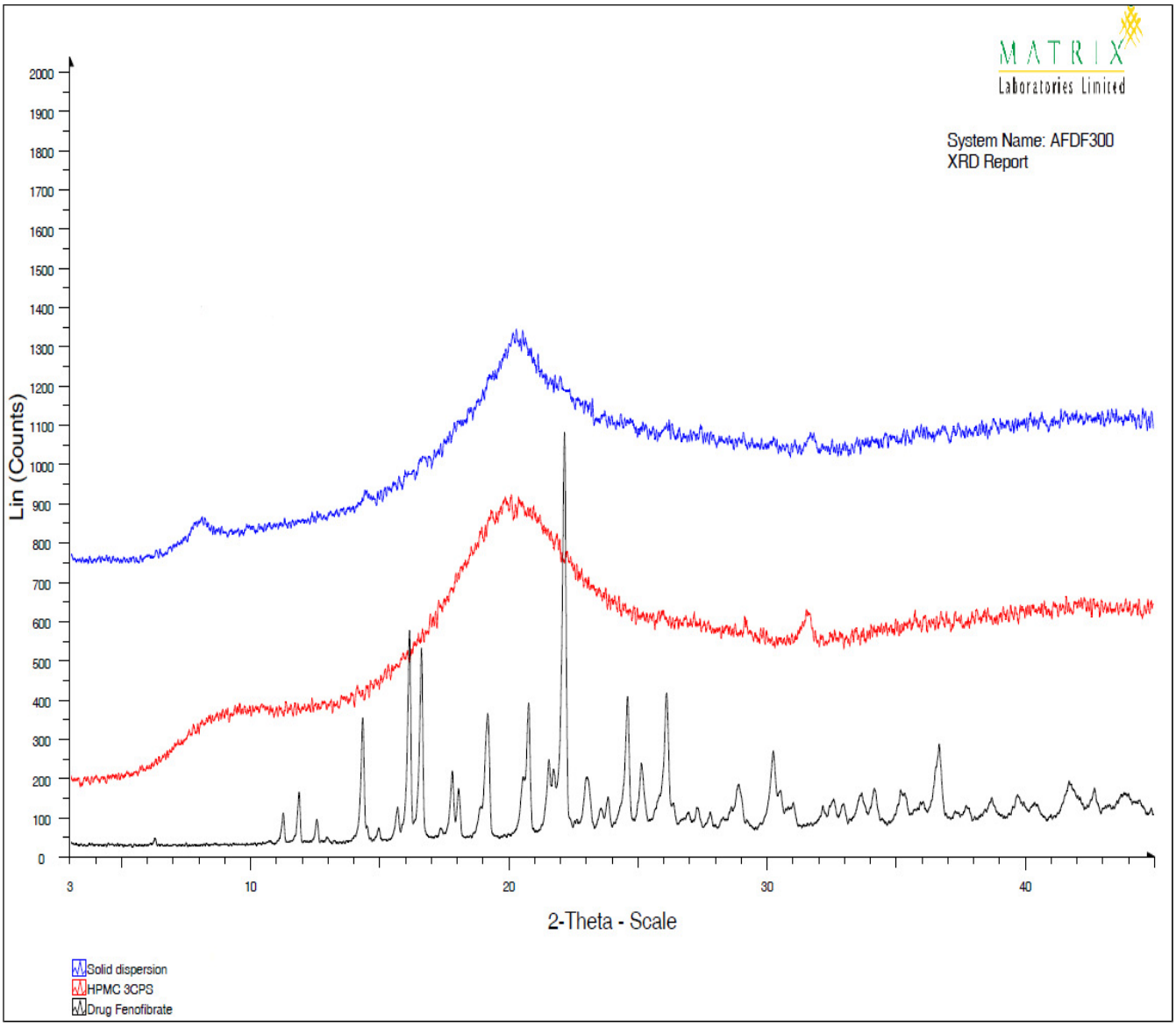


Figure 23: Overlay of XRD patterns of (a) solid dispersion (b) HPMC (c) PVP K30 (d) Fenofibrate

Inference: XRD Diffractogram of HPMC showed that the polymer is amorphous in nature. Pure drug has shown sharp crystalline peaks whereas solid dispersion has converted drug from crystalline to amorphous state which resulted in improved solubility and dissolution properties. Solid dispersion (SD 25) does not show any of the characteristic drug peaks indicating the amorphous nature of drug in the solid dispersion.

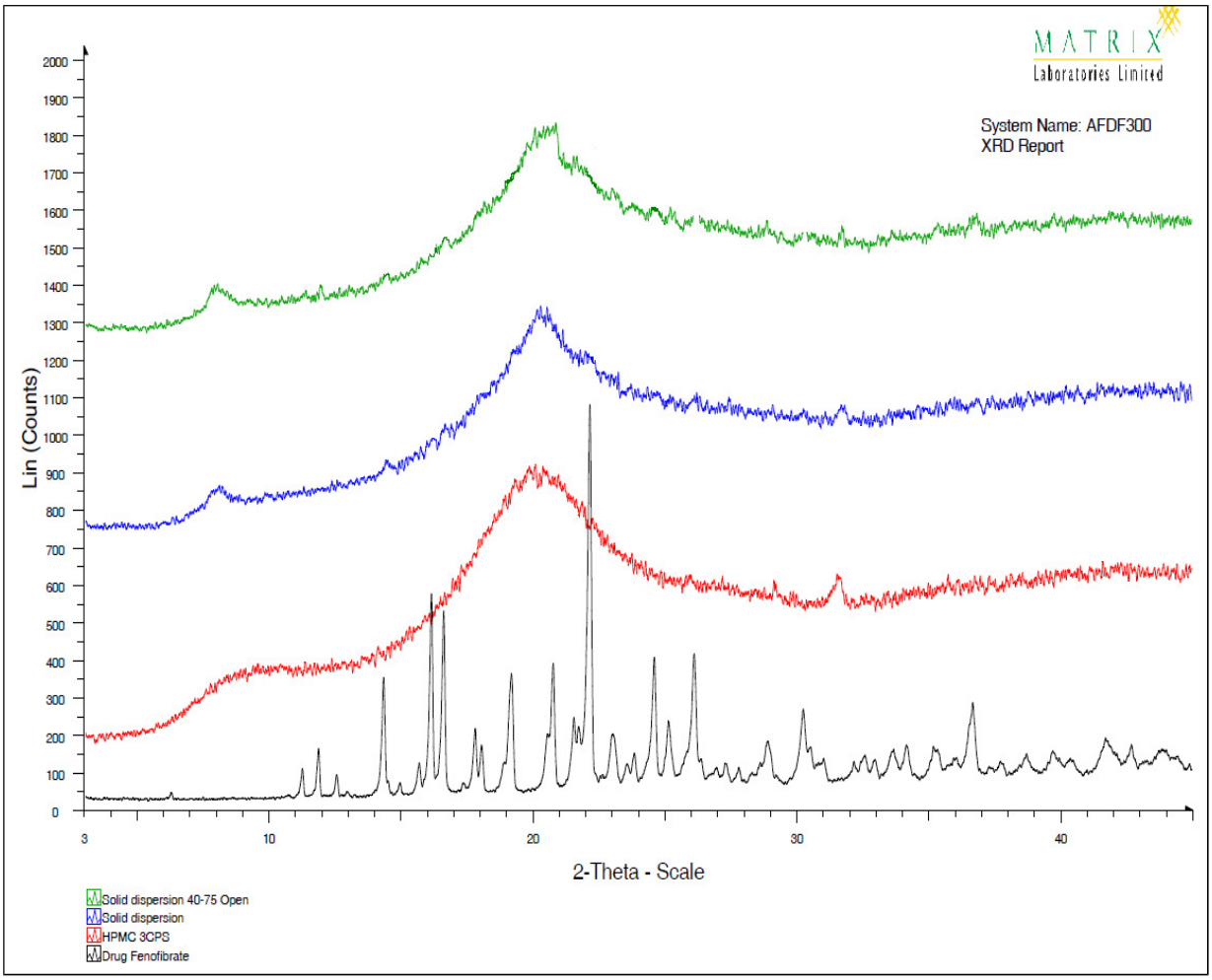


Figure no: 24 COMPARITIVE XRD OF DRUG SOLID DISPERSION (INITIAL) AND STABILITY SAMPLE OF SOLID DISPERSION (40^{0}C & 75%RH) Open Exposure

Inference: The x ray diffraction pattern of stability sample of solid dispersion(open exposure) is similar to initial Diffractogram indicating that the drug has not re crystallized after open exposure to high temperature and moisture.

Hence x-ray diffraction studies confirm the stability of the solid dispersion formulated by using HPMC 3cps as polymer**.**

10.3.3. Investigation of chemical interaction between drug and carrier in solid dispersion by FTIR:

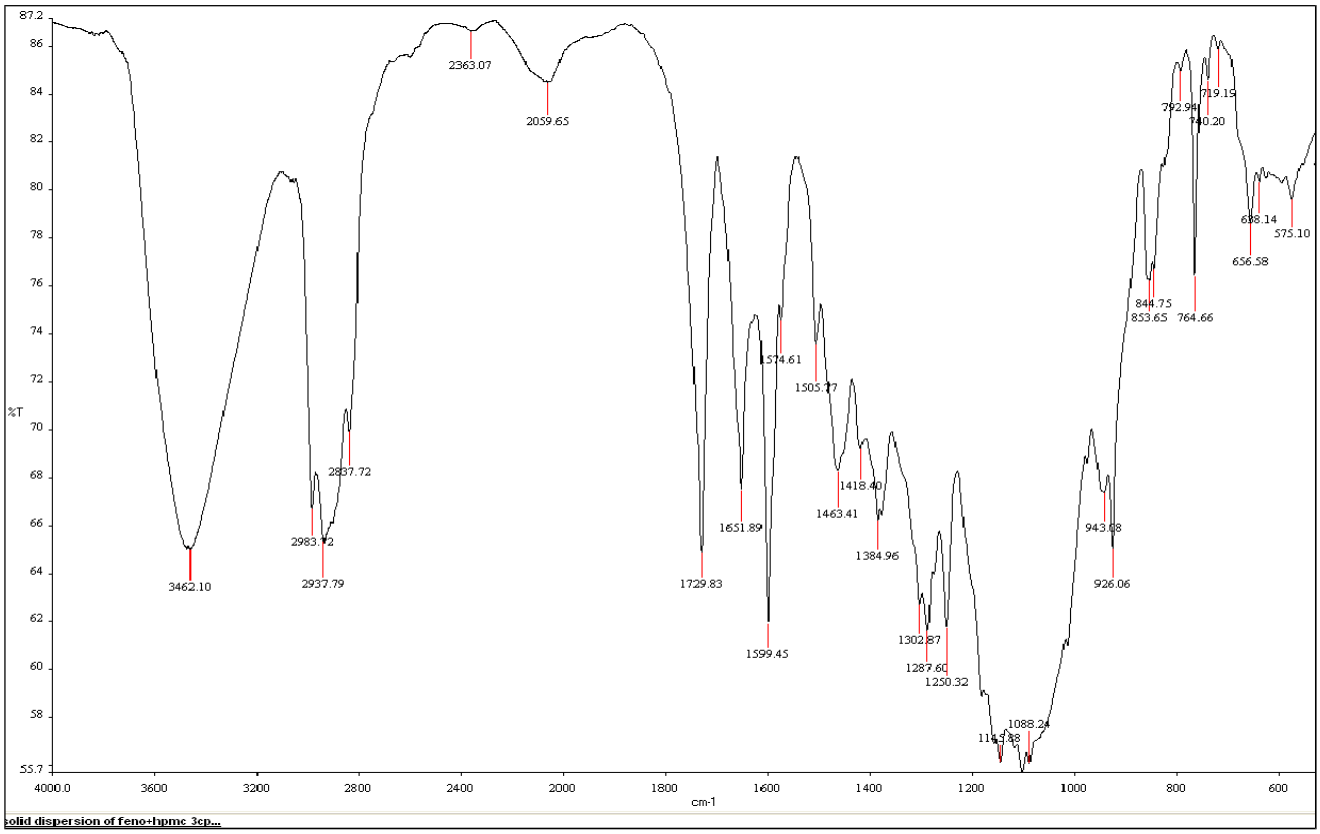


Figure no: 25 FT IR OF SOLID DISPERSION (SD 25) CONTAINING DRUG AND HPMC 3CPS

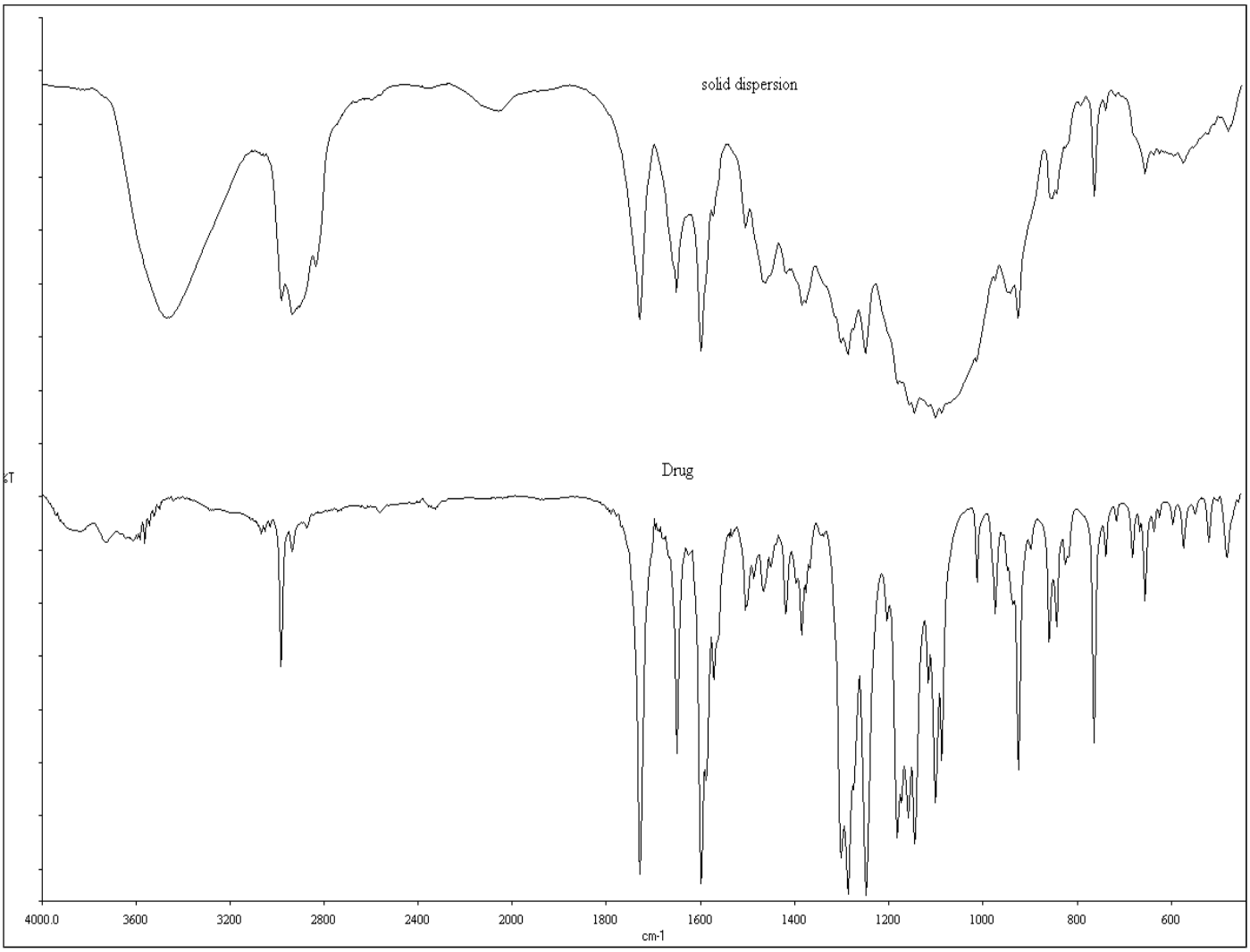


Figure 26: FTIR Spectrum of solid dispersion containing drug and HPMC 3cps and Fenofibrate

Inference: FTIR spectrum of Fenofibrate is not identical with FTIR spectrum of solid dispersion which indicates that there might be drug carrier interaction in solid dispersion which resulted in improved solubility of Fenofibrate

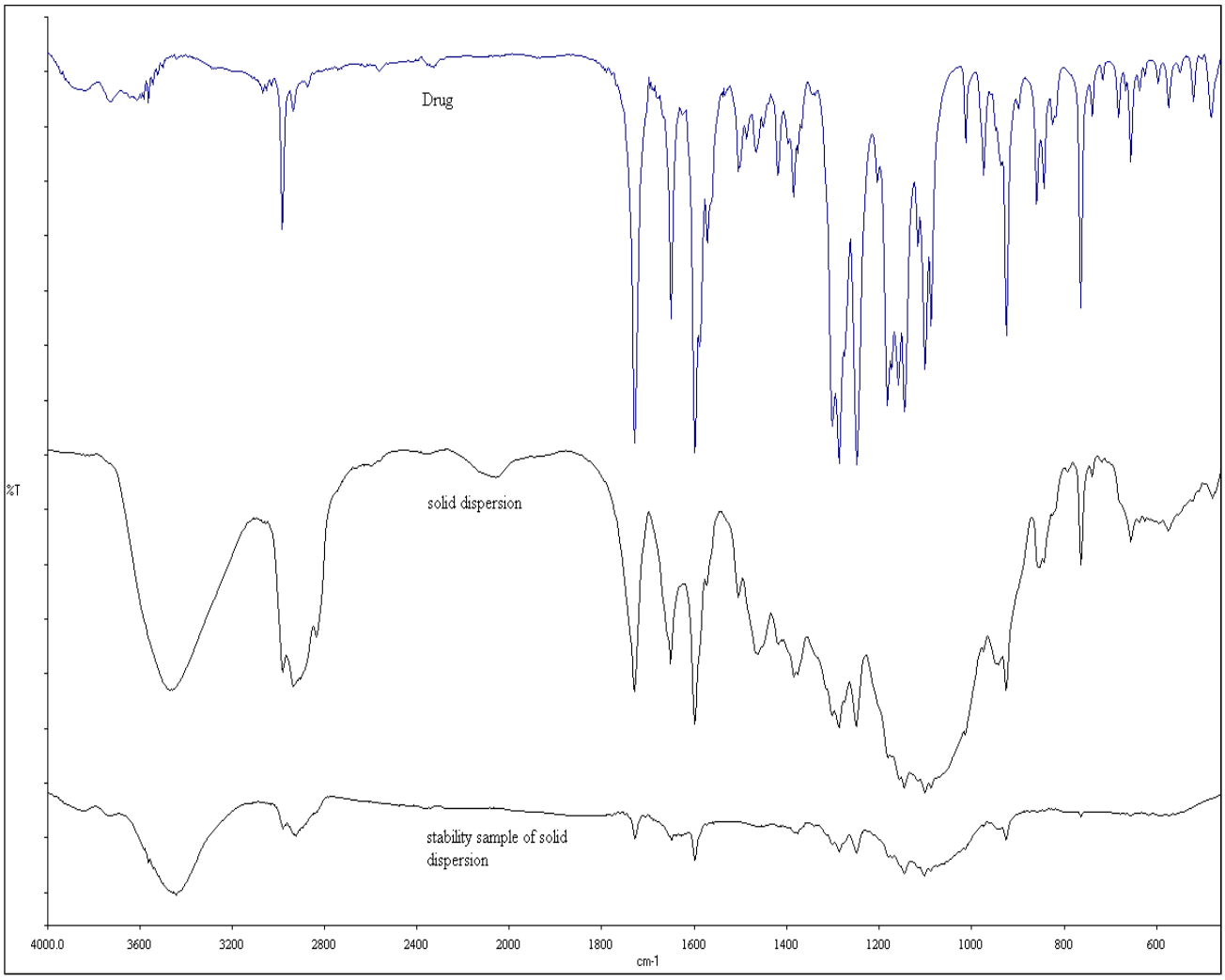


Figure 27: Overlay of FTIR spectrums of solid dispersion containing drug, HPMC, and Fenofibrate with the stability sample.

Inference: FT IR spectra of solid dispersion before and after exposure to high temperature and moisture levels are similar showing identical peaks. But the transparency of KBr pellet making varied which resulted in less depth of the peaks but the wave numbers are identical indicating that the solid dispersion is stable.

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10.4. Preformulation studies of tablet

10.4.1. Physical characterization of solid dispersion.

A).Particle size distribution:

Table 48: Particle size determination of solid dispersion

Sieve Mesh Number	Sieve Size Opening(µm)	Mass of Sample Retained on Each Sieve(g)	Percentage of Sample Retained on Each Sieve (%)	Cumulative Percentage of Sample Retained on Each Sieve (%)
20	841	0	0	0
40	420	0.02	0.4	0.4
60	250	0.86	17.2	17.6
80	177	1.26	20.2	37.8
100	149	0.49	9.8	47.6
120	125	0.9	13	60.6
Pan	-	1.47	49.4	100

Inference: From the particle size distribution data, it was observed that, 49.4 % of solid dispersion particles were found to be below of 125 microns in size.

10.4.2. Drug-Excipients compatibility studies:

Table 49: Visual observation for Solid dispersion-Excipient Ratios for Compatibility Study

Physical Appearance					
Composition Code	**Initial**	**I Week 40°C/75% RH**	**II Weeks, 40°C/75% RH**	**III Weeks, 40°C/75% RH**	**IV Weeks, 40°C/75% RH**
Solid dispersion	Cream White powder	NC	NC	NC	NC
Solid dispersion + Mannitol	Cream White powder	NC	NC	NC	NC
Solid dispersion+ lactose	Cream White powder	NC	NC	NC	NC
Solid dispersion+ Sorbitol	Cream White powder	NC	NC	NC	NC
Solid dispersion+ Ppxl	Cream White powder	NC	NC	NC	NC
Solid dispersion+ Mg sterate	Cream White powder	NC	NC	NC	NC

*NC- no change

10.5 DSC THERMOGRAMS OF SOLID DISPERSION - EXCIPIENT COMPATABILITY STUDY BEFORE AND AFTER EXPOSURE TO ACCELERATED CONDITIONS

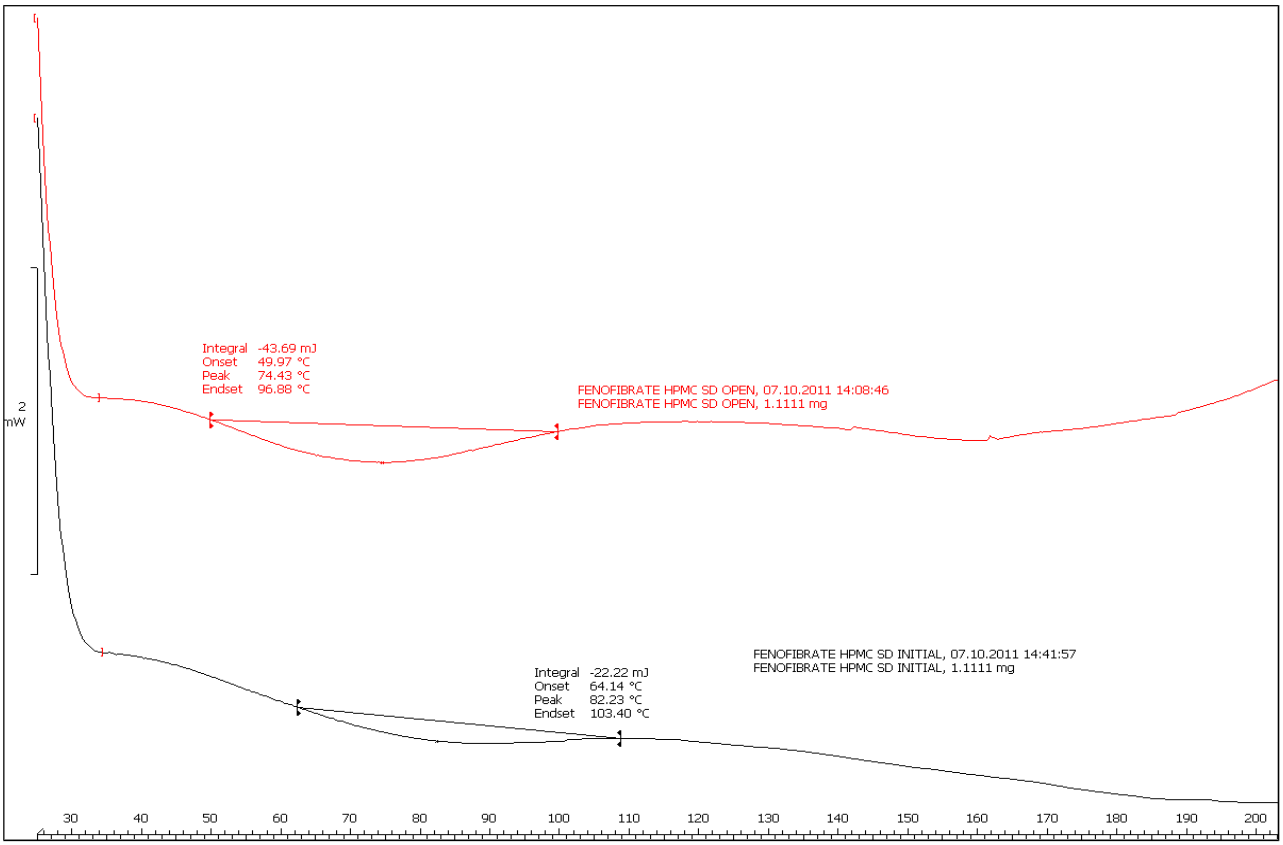


Figure no:28 DSC of solid dispersion before and after accelerated storage condition (40°C & 75% RH open exposure)

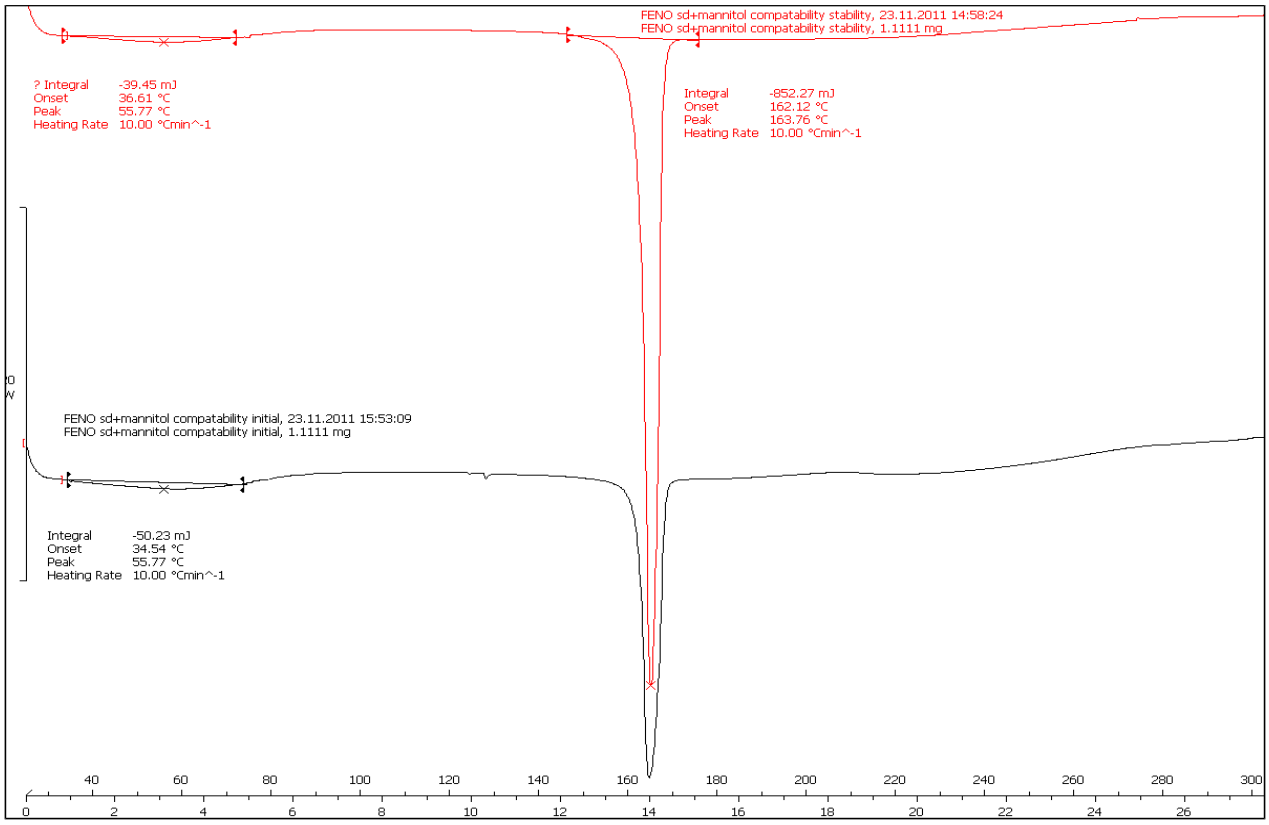


Figure no:29 DSC of solid dispersion and Mannitol physical mixture before and after accelerated storage condition (40ºC & 75% RH open exposure)

Inference:

DSC theromogram of the physical mixture of solid dispersion and mannitol before and after exposure to accelerated conditions of storage are similar. It indicates that the drug and the mannitol are compatible with each other and hence mannitol can be used for the formulation of ODT with the solid dispersion.

Thermogram also indicates the stability of the solid dispersion in the amorphous form.

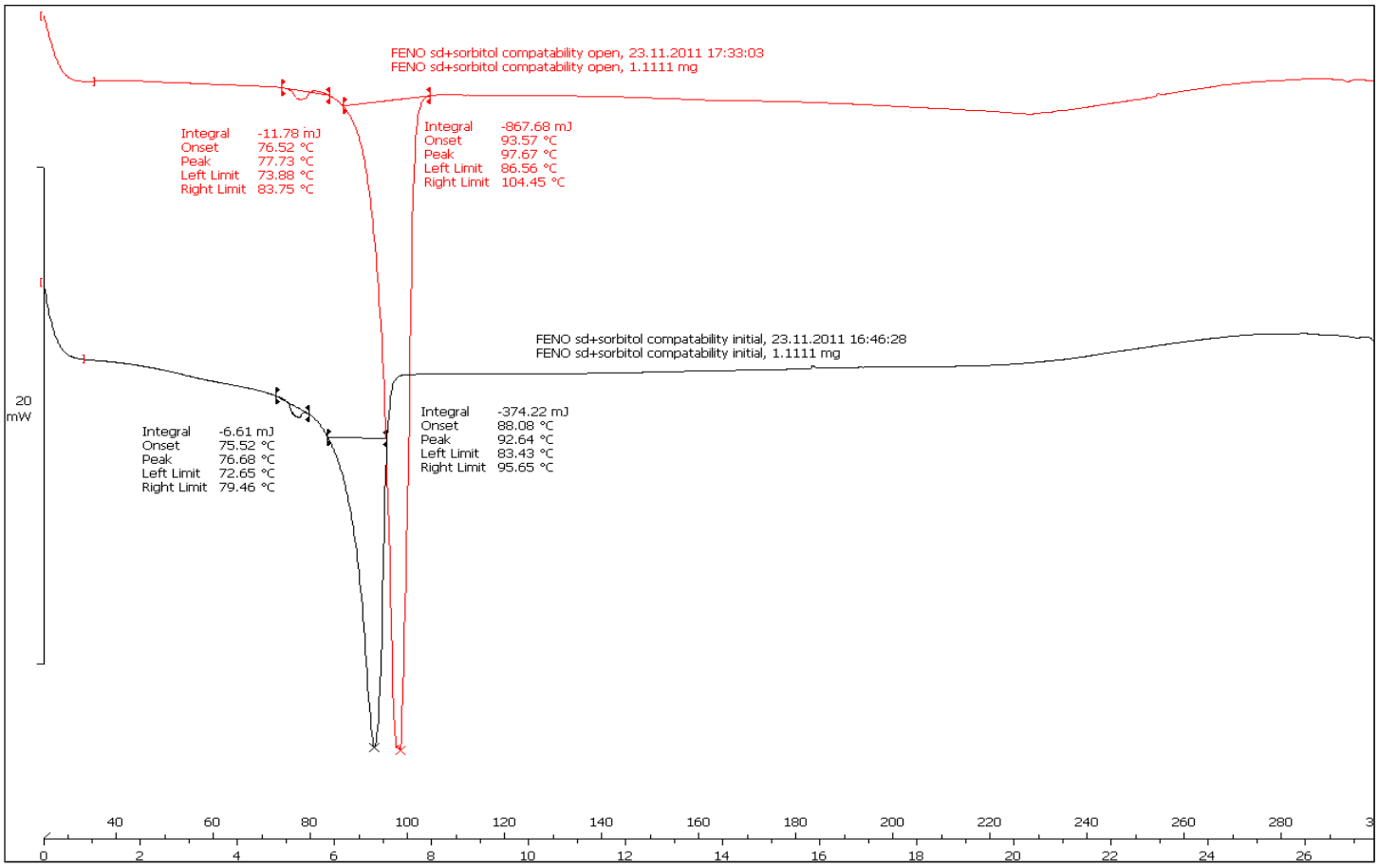


Figure no:30 DSC of solid dispersion and Sorbitol physical mixture before and after accelerated storage condition (40ºC & 75% RH open exposure)

Inference:

DSC theromogram of the physical mixture of solid dispersion and sorbitol before and after exposure to accelerated conditions of storage are similar. It indicates that the drug and the sorbitol are compatible with each other and hence sorbitol can be used for the formulation of ODT with the solid dispersion.

Thermogram also indicates the stability of the solid dispersion in the amorphous form.

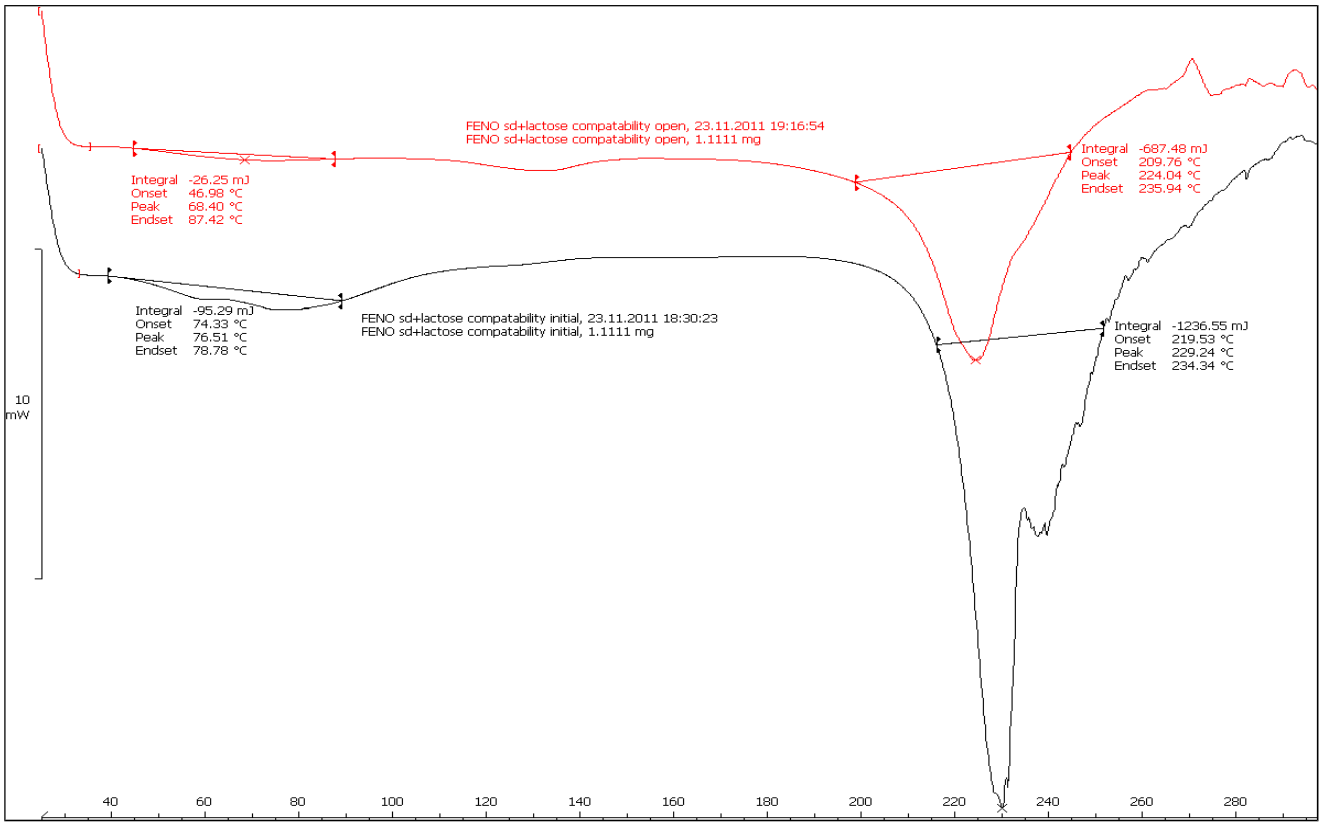


Figure no:31 DSC of solid dispersion and Lactose physical mixture before and after accelerated storage condition (40ºC & 75% RH open exposure)

Inference:

DSC theromogram of the physical mixture of solid dispersion and Lactose before and after exposure to accelerated conditions of storage are similar. It indicates that the drug and the Lactose are compatible with each other and hence Lactose can be used for the formulation of ODT with the solid dispersion.

Thermogram also indicates the stability of the solid dispersion in the amorphous form.

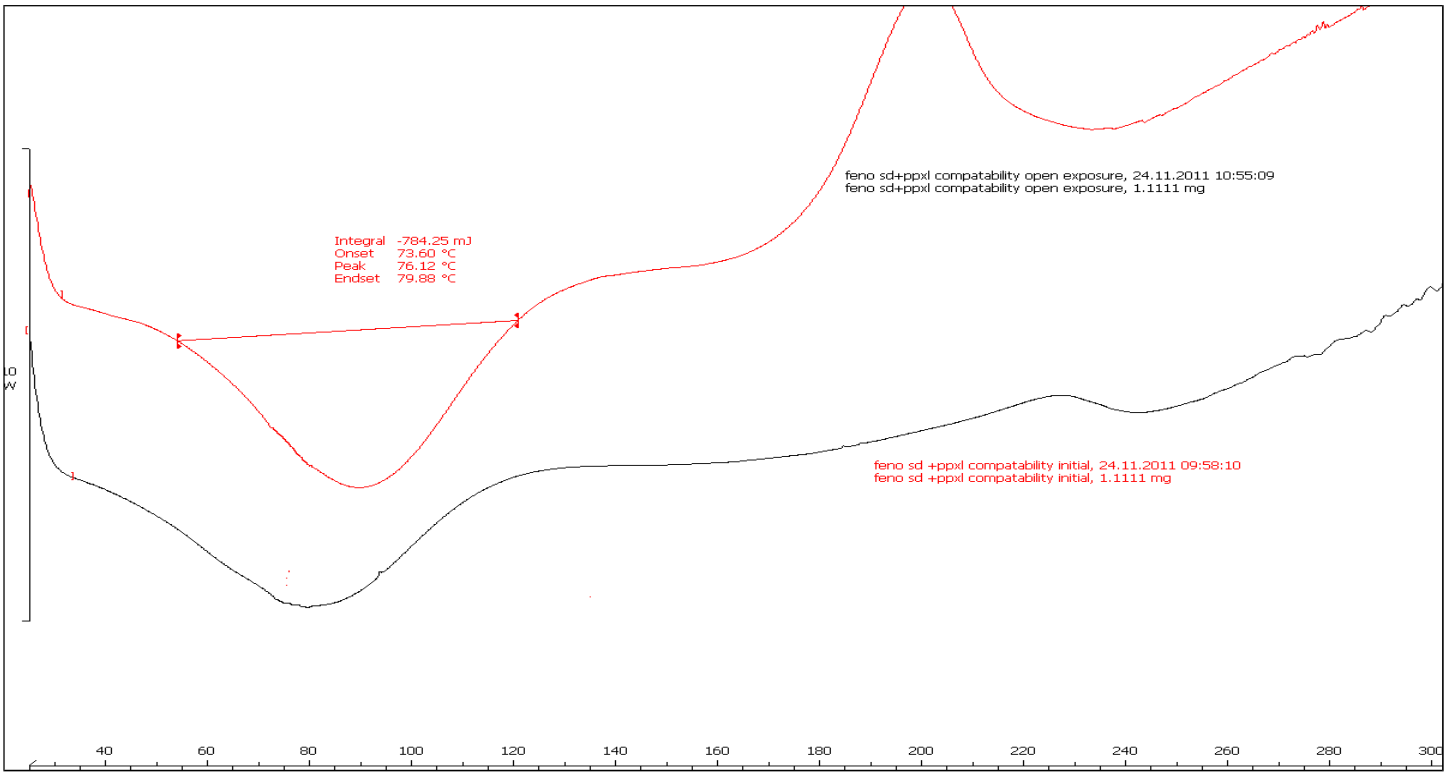


Figure no:32 DSC of solid dispersion and polyplasdone XL physical mixture before and after accelerated storage condition (40°C & 75% RH open exposure)

Inference:

DSC theromogram of the physical mixture of solid dispersion and polyplasdone XL before and after exposure to accelerated conditions of storage are similar. It indicates that the drug and the polyplasdone XL are compatible with each other and hence polyplasdone XL can be used for the formulation of ODT with the solid dispersion.

Thermogram also indicates the stability of the solid dispersion in the amorphous form.

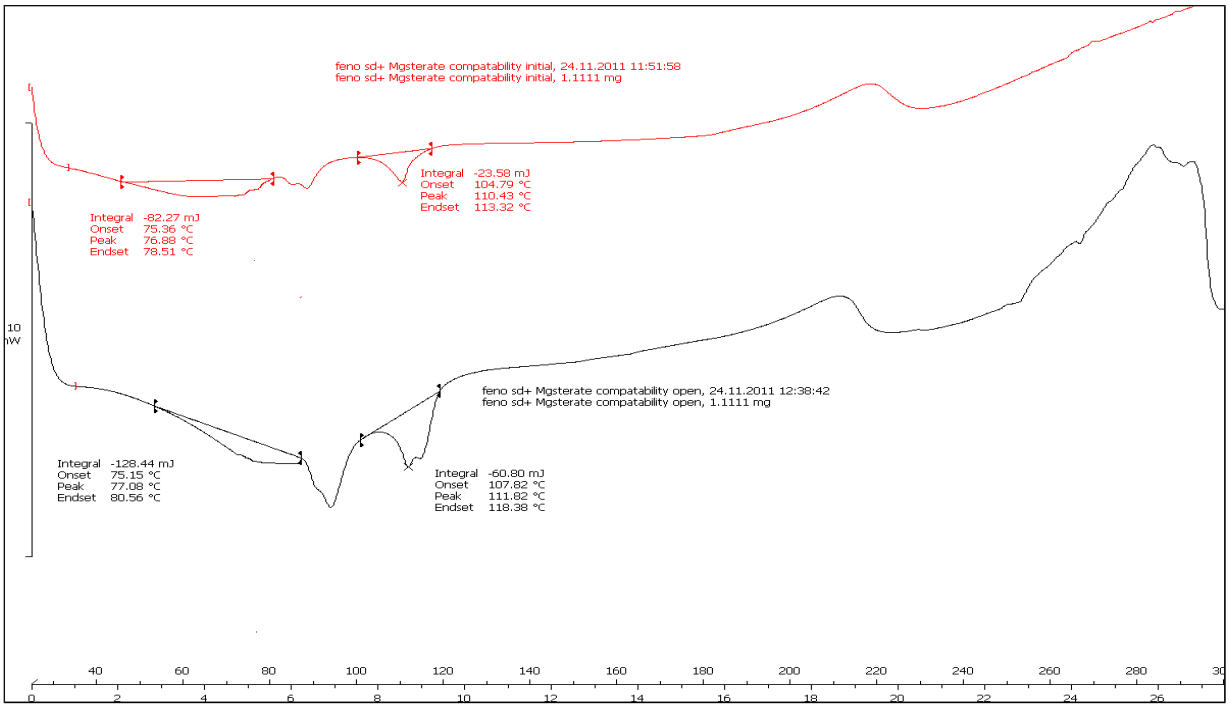


Figure no:33 DSC of solid dispersion and Magnesium stearate physical mixture before and after accelerated storage condition (40ºC & 75% RH open exposure)

Inference:

DSC theromogram of the physical mixture of solid dispersion and Magnesium stearate before and after exposure to accelerated conditions of storage are similar. It indicates that the drug and the Magnesium stearate are compatible with each other and hence Magnesium stearate can be used for the formulation of ODT with the solid dispersion.

Thermogram also indicates the stability of the solid dispersion in the amorphous form.

10.6 EVALUATION PARAMETERS

10.6.1 Blend Characterization

Table 50: Blend characterization of formulations of trial batches

Formulation Code	Tapped Density (gm/cm^3)	bulk density (gm/cm^3)	Compressibility Index (CI) (%)	Hausner ratio (HR)	Angle of repose (θ)	PSD (in µ)
F1	0.36	0.33	9.09	1.09	26.2	11-12
F2	0.37	0.34	8.11	1.09	25.7	12-13
F3	0.39	0.35	10.25	1.11	33.5	11-12
F4	0.36	0.32	11.11	1.13	31.7	11-12
F5	0.34	0.31	8.82	1.10	28.4	13-14
F6	0.36	0.31	13.88	1.16	24.8	12-13

Inference:

The granules prepared for compression of tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in Table-49.

The formulations showed good flow property and Carr's index. Angle of repose ranged from 24.7^0 to 33.5^0 and the Carr's index ranged from 9.09 to 13.88. The Bulk Density and Tapped Bulk Density of the prepared granules ranged from 0.3 to 0.354g/cc and 0.33 to 0.39 g/cc respectively. The results of angle of repose indicates good flow property of the granules and the value of Carr's compressibility index further showed support for the flow property.

10.6.2 EVALUATION OF ORAL DISINTEGRATING TABLETS

Table 51: Physical parameters of tablets of trial batches

Formulation code	Target weight (mg)	Weight variation (%)	Thickness (mm)	Friability (%)
F1	350	± 1.68	4.11± 0.2	0.72 ± 0.03
F2	350	± 1.37	4.09± 0.1	0.67 ± 0.09
F3	350	± 0.51	4.11± 0.1	0.74 ± 0.03
F4	350	± 0.49	4.12± 0.1	0.65 ± 0.02
F5	350	± 0.55	3.08± 0.3	0.76 ± 0.12
F6	350	± 1.68	4.11± 0.2	0.84 ± 0.02

Table 52 Physicochemical parameters of oral disintegrating tablets of trial batches

Formulation code	% drug content
F1	98.74 ± 0.42
F2	97.12 ± 0.63
F3	99.37 ± 0.51
F4	96.21 ± 0.23
F5	98.28 ± 0.36
F6	96.37 ± 0.45

Inference: The variation in weight was within the range of ±7.5% complying with pharmacopoeial specifications . The thickness of tablets was found to be between 4-5 mm. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet.

The percentage drug content varied between 97 to 99.37% in different formulations indicating content uniformity in the prepared batches

10.7 EFFECT OF MOISTURE TREATMENT ON HARDNESS AND DISINTEGRATION TIME OF THE FORMULATIONS

10.7.1 Effect of formulation hardness on the disintegration time of the tablet before moisture treatment:

Formulation	Hardness 1 to 2 kp	Hardness 2 to 3 kp
F1	1 min 54sec	3 min 58sec
F2	1 min 30sec	3 min 21sec
F3	1 min 42sec	3 min 28sec
F4	26sec	1 min 10sec
F5	20sec	45sec
F6	14sec	30sec

Table 53: Effect of formulation hardness on the disintegration time

10.7.2 Effect of moisture treatment on Hardness:

Moisture exposed	Hardness
33%RH	Increased up to 2 kp
53%RH	No effect on hardness
84%RH	Softening of tablet, hardness below 1 kp

Table 54: Effect of moisture treatment on Hardness

10.7.3 Effect of moisture treatment on Disintegration time:

Moisture exposed	Disintegration time
33%RH	Increased from 1 min to 2 min
53%RH	Decreased from 3 min to 2 min 20sec
84%RH	Very less 4 to 5sec

Table 55: Effect of moisture treatment on DT

Inference:

Based on the results obtained after moisture treatment it was found that

1. When exposed to low moisture condition (33%RH) tablets hardness is considerably increased (up to 2kp) and disintegration time also increased because of increased hardness. The reason for increased hardness is that at low moisture levels tablets absorb sufficient

moisture to form liquid bridges that will be converted to solid bridges between the molecules on drying that led to the increase in the hardness and as a result DT is also increased.

2. When exposed to optimum moisture condition (53%RH) hardness has no influence on the hardness of the tablet and DT decreased.

3. When exposed to high moisture condition (84%RH) tablets got softened and DT was very low because of softening. The reason for softening was due to formation of too many liquid bridges between the molecules because of high moisture levels. Even on drying the tablets hardness was not increased.

The amount of super disintegrant in the formulation also influences the hardness and DT during the moisture treatment.

Amount of super disintegrant for the optimized formulation was chosen as 5mg/tab because high amount of super disintegrant may lead to softening of tablet on moisture treatment.

Hence the optimized formulation is chosen as the one containing

Hardness – 2- 3 KP

Moisture treatment - 53%RH

DT – 20 to 30 sec

Because at 2 to 3kp the tablets will be sufficiently hard for blister packing and bottle packing also. Moisture exposure to 53%RH may not affect the hardness but DT will be sufficiently lowered because of formation of liquid bridges. The amount of super disintegrant was chosen as 5mg/tab to enhance the disintegration of the tablet**.**

Optimized formulation (F4) based on Hardness, Disintegration time, and Moisture treatment:

Ingredients	**Amount (mg/tab)**
Solid dispersion	160
Mannitol	162
Sorbitol	18
Polyplasdone XL	5
Magnesium stearate	5

Ethanol	q.s
Total	350

Table no: 56 Optimum formula

Parameters of optimized formulation before and after Moisture treatment (53%) RH:

Evaluated parameters	Before moisture treatment	After Moisture treatment
Weight of tablet	350mg	353mg
Hardness	2 to 2.5 kp	2 to 3 kp
Disintegration time	56sec	28sec

Table no: 57 Effect of moisture treatment

10.8 In vitro dissolution studies:

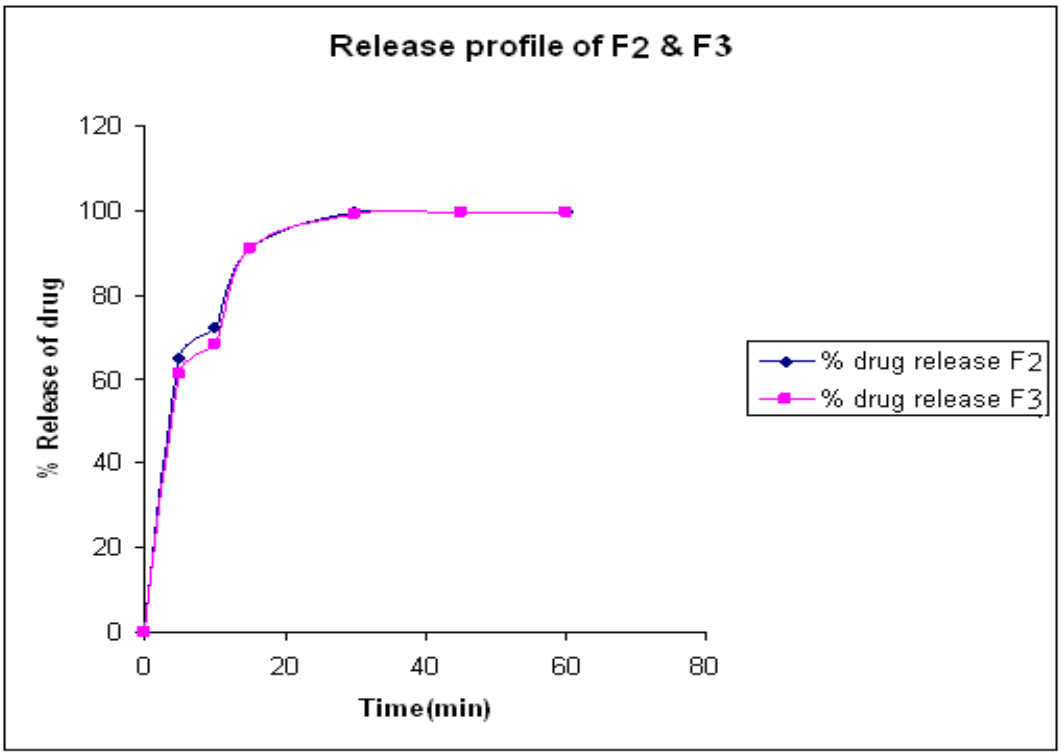
10.8.1 In vitro drug release from formulation f2 and f3 in 0.5%sls in water media

Time (min)	% drug release	
	F2	F3
5	65.1	61.1
10	72	68.4
15	91.1	90.8
30	99.4	99.2

45	99.5	99.4
60	99.3	99.5

Table 58: In vitro drug release

Figure no: 34



Inference:

The %drug release was not that influenced by Mannitol or Lactose. Although there was an slight initial lag in release of drug on use of lactose than use of Mannitol. Hence Mannitol was chosen for further formulations as the final drug release percentage was same.

10.8.2 Comparision of In vitro dissolution studies of optimized formulation and pure drug in Different pH conditions:

Table 59: Dissolution profile in pH 1.2 buffer

Time (min)	Fenofibrate tablet	Optimized formulation
5	6.8	11.65
10	7.2	17.52
15	8.43	21.22
30	8.44	24.7
45	8.41	26.8
60	8.52	26.9

Figure no: 35

10.8.3 Dissolution profile in pH 4.5 buffer

Table 60: In vitro drug release in 4.5 buffer

Time (min)	Fenofibrate tablet	Optimized formulation
5	5.2	13.2
10	6.1	16.8
15	6.8	18.2
30	6.9	26.7
45	6.7	30.4
60	6.4	30.2

Figure no: 36

10.8.4 Dissolution profile in pH 6.8 buffer

Time (min)	Fenofibrate tablet	Optimized formulation
5	4.1	16.5
10	4.8	21.7
15	6.2	27.4
30	7.1	36.1
45	7.5	42.5
60	7.6	42.1

Table 61: In vitro drug release in 6.8 medium

Figure no:37

Inference:

The amount of drug release from the solid dispersion in optimized formulation was higher in all pH conditions compared to the pure drug in the formulation. The release rate was found to 42% at the end of 45 min in 6.8 phosphate buffer while the pure drug has shown only 7.6% of release.

The drug release was found to be stabilized after certain time points indicating that the max solubility (saturation solubility) of the drug in the medium has been reached.

The release profile of the drug has been significantly enhanced by formulating as solid dispersion than that of pure drug.

10.8.5 Dissolution profile in 0.5% sls in water

Time (min)	Fenofibrate tablet	Optimized formulation
2	14.8	64.2
5	40.17	67.9
10	48.61	71.4
15	52.7	92.4
30	55.84	99.8
45	57.05	99.9
60	61.4	99.7

Table 62: In vitro drug release from dissolution medium

Figure no: 38

Inference:

The optimized formulation has shown 99% drug release from the solid dispersion at the end of 30mins compared to only 61% of drug release from the pure drug formulation at the end of 60mins.

Hence the drug release will be better by using drug as solid dispersion rather than using drug as such in the formulation for the hyper lipidemic patients.

10.9 Accelerated Stability study of the optimized batch

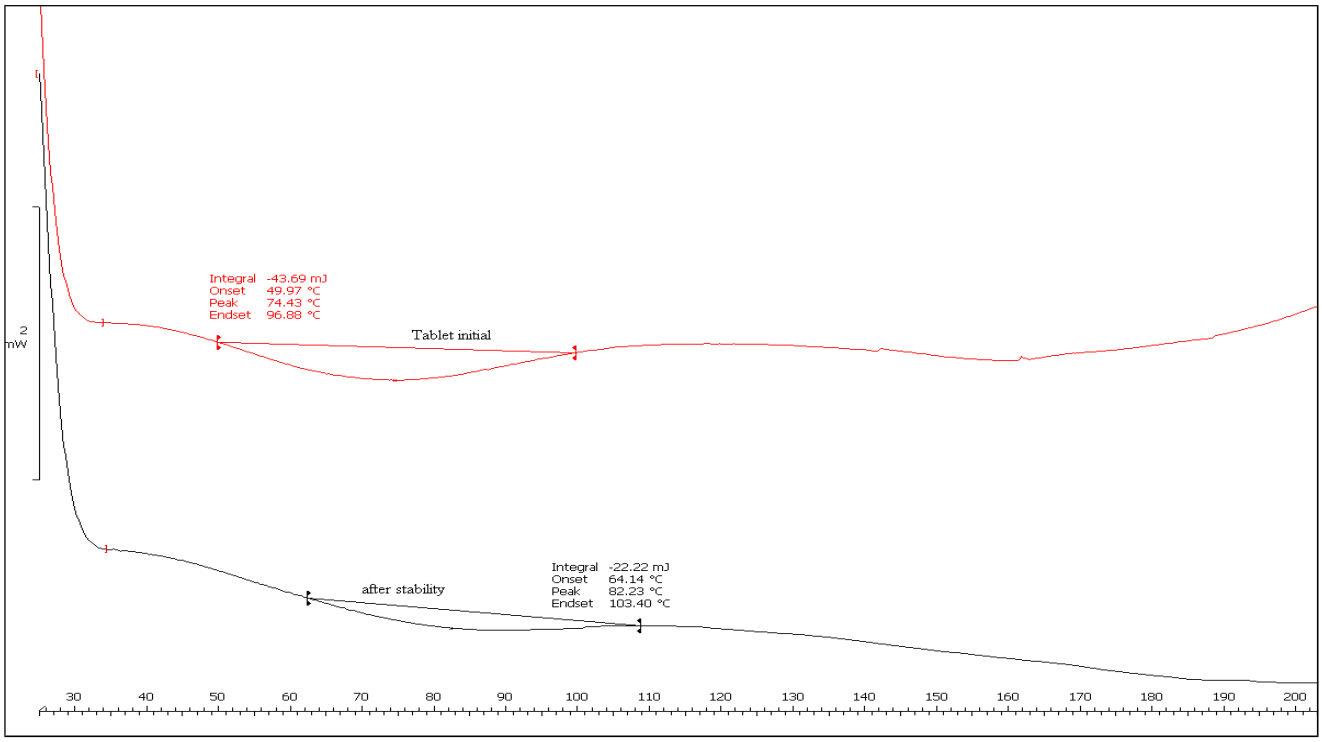


Figure no: 39

Table 63: Stability studies at 40^0C and 75%RH

PARAMETER	Initial	30th Day
COLOUR	White	No change
WEIGHT	350+/-5 mg	350+/-5mg
ASSAY	99%	98.1%
% RELEASE	98.9% at end of 45 min	97.6% at end of 45 min

Table 64: Stability studies at 25^0C and 60%RH

PARAMETER	Initial	30th Day
COLOUR	White	No change

WEIGHT	**350+/-5 mg**	**350+/-5mg**
ASSAY	**99.2%**	**98.1%**
% RELEASE	**99% at end of 45 min**	**97.9% at end of 45 min**

Inference:

There was no drug peak even after the exposure of the final tablet to accelerated conditions of temperature and humidity. Hence the final formulation is found to be stable

The tablet has been stable even after exposure to accelerated condition

Assay and percentage release even after exposure to accelerated conditions are with in the limits indicating stability of formulation

XI. SUMMARY AND CONCLUSION

The main aim of present study is to develop a rapidly dissolving tablet of Anti hyperlipidemic drug using saccharides for better mouth feel and improving patient compliance. The solubility of pure drug is very low in all the pH conditions hence in order to improve the solubility drug is converted in to solid dispersion.

Solid dispersion's are prepared by using polymers PVP K90, soluplus, kollicoat IR, HPC SSL and HPMC 3cps by solvent evaporation method. Out of 5 polymers only soluplus and HPMC has shown a change in the crystalline nature of the drug to amorphous form as indicated by the DSC thermogram

Hence solid dispersion prepared by using soluplus and HPMC in various ratios 1:0.5, 1:1, 1:2, 1:3, 1:4 by both solvent evaporation and melt fusion method to find the effect of method of preparation on the solubility enhancement.

Solvent evaporation method has produced better solubility in the case of soluplus but the formulation has failed in the stability studies showing drug peak in the DSC thermogram. On the other hand with HPMC melt fusion method has shown better solubility and the formulation is found to be stable as shown by the DSC, XRD and FTIR studies. Hence drug and HPMC in 1:4 ratio formulated by melt fusion method is chosen as optimized solid dispersion

By using optimized solid dispersion oral disintegrating tablets of 6 formulations have been prepared to optimize the concentration of super disintegrant needed to attain the desired disintegration time. Tablets compressed at two different hardness levels 1-2 kp and 2-3 kp are exposed to 3 different moisture conditions (33%, 53%, 84%RH) to optimize the level of moisture needed for attaining sufficient hardness and DT.
53%RH was found to be optimum that slightly increases the hardness and lowers the DT below 30sec with 5mg/tab of super disintegrant compressed at 2 KP hardness.

The drug release from the optimized formulation was compared with that of the pure drug in all pH conditions and is found to be better from the solid dispersion rather than the pure drug.

Optimized formula has shown a release of 99% at the end of 30mins where as release from pure drug formulation is only 60% at the end of 60min.

Formulation of ODT by WOWTAB technology using solid dispersion technique has produced better drug release and good mouth feel and can enhance the patient compliance of geriatric and pediatric hyperlipidemic patients.

XII. BIBLIOGRAPHY

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