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SOLUBILITY ENHANCEMENT OF FENOFIBRATE BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Fenofibrate is a lipid lowering drug used in the treatment of hyperlipidemia, which is not soluble in water and lower absorption in gastric fluid. In order to improve the solubility and oral absorption of the drug in gastric fluid to enhance solubility of drug by using solid dispersions technique. Solid dispersions of Fenofibrate were prepared and evaluated by using β-cyclodextrin in different ratios (1:1, 1:2, 1:3, 1:4, 1:5). The effect of kneading method of preparation of solid dispersion on solubility behavior was also investigated. Solid dispersions containing Fenofibrate/β-cyclodextrin formulation provide a promising way to enhance solubility of fenofibrate. In the formulations of the Fenofibrate and Beta cyclodextrin, Formulation (1:5) shows the great enhance in solubility than pure drug. Beta-cyclodextrin was chosen as the carrier because it has high hydrophilicity, non-toxic, inert, economical. thus the solubility and bioavailability of fenofibrate was enhanced by the preparation of solid dispersion by kneading method.

KEYWORDS

Solubility, solid dispersion, Fenofibrate, Beta-cyclodextrin, Kneading method.

1.INTRODUCTION [1-2]

Solubility is one of the most important physicochemical properties of any drug becauselow solubility can affect the bioavailability of orally administered dosage form. Thus,it is very important to enhance the solubility of poorly soluble drug. Solubility is not to be confused with the ability to dissolve or liquefy a substance, since this process may occur not only because of dissolution but also because of a chemical reaction. Low aqueous solubility is the major problem encountered with

formulation development of new chemical entities as well as for the generic development. More than 40% of new chemical entities developed in pharmaceutical industry are lipophilicand fail to reach the market due to their poor water solubility. The solubility behaviorof drug is the major challenge for formulation scientist.

1.1. Solubility: [3-4]

Solubility is the property of a solid, liquid, or gaseous chemical substances called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solutionof the maximum quantity of solute in a certain quantity of solvent at specified temperature and pressure. The term solubility is defined as maximum amount of solute that can be dissolved in a given amount of solvent. Quantitatively it is defined as the concentration of solute in a saturated solution at a certain temperature. In qualitative terms, solubility may be defined as the spontaneous interaction of two or more substances to form homogeneous molecular dispersion. The substances to be dissolvedare called as solute. The process of dissolving solute into solvent is called as solution orhydration if the solvent is water. The study of solubility enhancement is mainly studied on drug which has low aqueous solubility and high permeability.

Any drug is said to be poorly soluble when:

Aqueous solubility < 100µg/ml

High crystal energy (melting point > 200˚ C)

Poor dissolution: Intrinsic dissolution rate < 0.1 mg/cm

High molecular weight (>500), Self-Association and aggregation

1.1.1. Expressing Solubility and Concentration:[5]

The solubility of the drug is described in various descriptive terms which is based on the amount of drug dissolve in the solvent and discussed in Table 1.1.

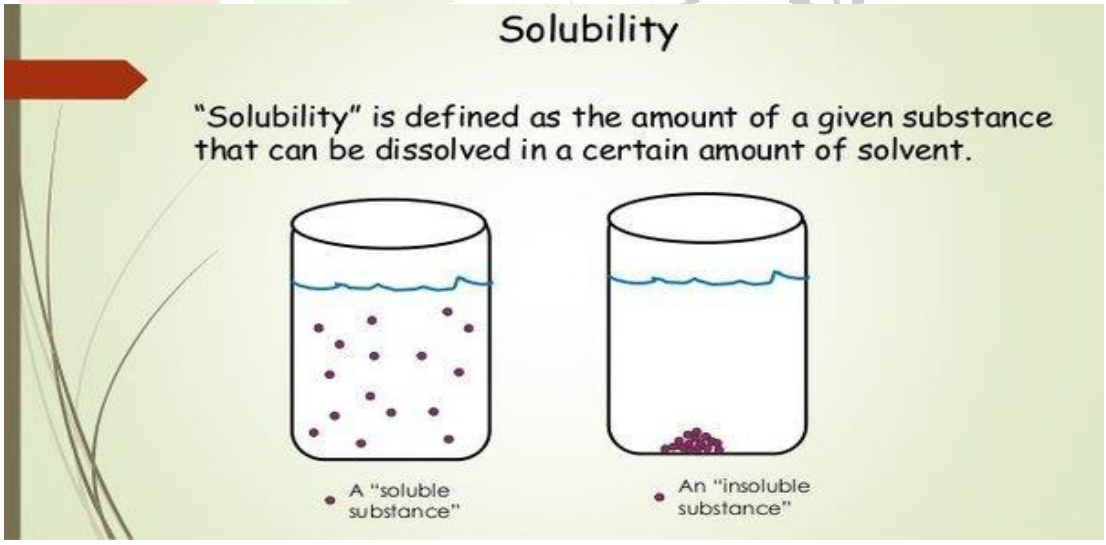


Figure no. 1.1. Solubility[8]

Table 1.1 Descriptive terms for solubility [8]

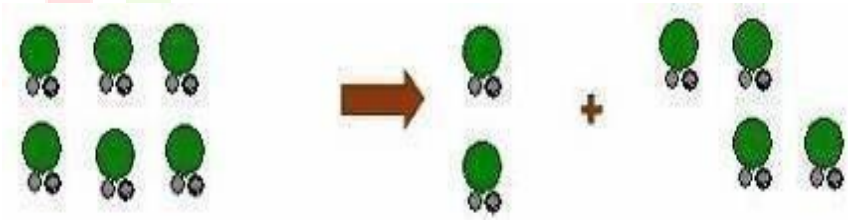
Descriptive term	Part of solvent required per partof solute
Very soluble	Less than 1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10000
Practically insoluble	More than 10000

Process of solubilization [6]

The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.

Step1: Holes opens in the solvent

Step2: Molecules of the solid breaks away from the bulk



Step 3: The freed solid molecule is integrated into the hole in the solvent

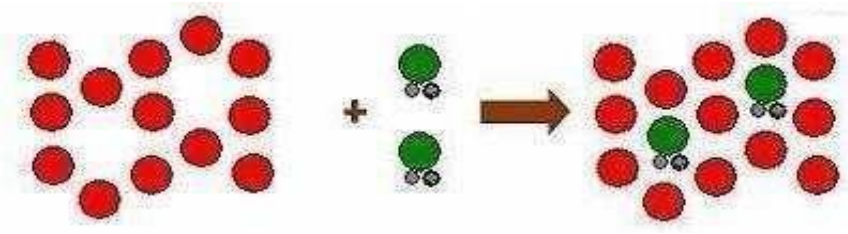


Fig No. 1.2. Process of solubilization[8]

1.2. Factors affecting solubilization:

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

1. Particle size [11]

The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent.

2. Temperature [11,13]

Temperature will affect solubility. If the solution process absorbs energy, then the solubility will be increased as the temperature is increased. If the solution process releases energy, then the solubility will decrease with increasing temperature. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases.

3. Pressure [14]

For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure havepractically no effect on solubility.

4. Nature of the solute and solvent

While only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at roomtemperature, 200 grams of zinc chloride can be dissolved. The great difference in the solubilities of these two substances is the result of differences in their nature.

5. Molecular size

The larger the molecule or the higher its molecular weight the less soluble the substance. Larger molecules are more difficult to surround with solvent molecules in order to solvate the substance. In the case of organic compounds, the amount of carbonbranching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.

6. Polarity

Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, thenpositive ends of solvent molecules will attract negative ends of solute molecules. Thisis a type of intermolecular force known as dipole-dipole interaction.

7. Polymorphs [18]

A solid has a rigid form and a definite shape. The shape or habit of a crystal of a givensubstance may vary

but the angles between the faces are always constant. A crystal ismade up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. This repeating pattern is known as the unit cell. The capacity for a substance to crystallize in more than one crystalline form is polymorphism.

1.3. Techniques of Solubility Enhancement:

There are various techniques available to improve the solubility of poorly solubledrugs.

a. Physical Modifications
b. Particle size reduction
c. Micronization
d. Nano suspension
e. Homogenization

a. Particle size reduction

Particle size reduction can be achieved by micronization and nanosuspension. Each technique utilizes different equipments for reduction of the particle size.

b. Micronization

The solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improves the dissolution properties of the drug. Conventional methods of particle size reduction, such as comminution and spraydrying, rely upon mechanical stress to disaggregate the active compound. The micronization is used to increased surface area for dissolution.

c. Nanosuspension [25,26]

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, whichare stabilized by surfactants [12]. The advantages offered by nanosuspension is increased dissolution rate is due to larger surface area exposed, while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor.Techmiques for the production of nanosuspensions.

d. Homogenization [27]

The suspension is forced under pressure through a valve that has nano aperture. This causes bubbles of water to form which collapses as they come out of valves. This mechanism cracks the particles. Three types of homogenizers are commonly used suchas conventional homogenizers, sonicators, and high shear fluid processors.

e. Wet milling

Active drug in the presence of surfactant is defragmented by milling. The nanosuspension approach has been employed for drugs including Tarazepide, Atovaquone, Amphotericin B, Paclitaxel and Bupravaquone. All the formulations arein the research stage. One major concern related to particle size

reduction is the eventual conversion of the high-energy polymorph to a low energy crystalline form, which may not be therapeutically active one. Drying of nanosuspensions can be doneby lyophilization or spray drying.

Other Techniques for Reduction of the Particle Size [31-36]

A. Sonocrystallization

Recrystallization of poorly soluble materials using liquid solvents and antisolvents hasalso been employed successfully to reduce particle size. The novel approach for particle size reduction on the basis of crystallization by using ultrasound is Sonocrystallization.

B. Supercritical fluid process

Novel nanosizing and solubilization technology whose application has increased particle size reduction via supercritical fluid (SCF) processes. A supercritical fluid (SF) can be defined as a dense noncondensable fluid. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp). The most widely employed methods of SCF processing for micronized particles are rapid expansion of supercritical solutions (RESS) and gas antisolvents recrystallization (GAS), both of which are employed by the pharmaceutical industry using carbon dioxide (CO2) as the SCF due to its favourable

processing characteristics like its low critical temperature (Tc = -31.1°C) and pressure(Pc = 73.8bar).

C. Spray drying

Spray drying is a commonly used method of drying a liquid feed through a hot gas. Typically, this hot gas is air but sensitive materials such as pharmaceuticals and solvents like ethanol require oxygen-free drying and nitrogen gas is used instead. Theliquid feed varies depending on the material being dried and is not limited to food or pharmaceutical products and may be a solution, colloid or a suspension. This process of drying is a one-step rapid process and eliminates additional processing. Spray dryingof the acid dispersed in acacia solutions resulted in as much as a 50% improvement in solubility of poorly water soluble salicylic acid.

D. Modification of the crystal habit

Polymorphism is the ability of an element or compound to crystallize in more than onecrystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture, stability etc. Broadly polymorphs can be classified as enantiotropes and monotropes based on thermodynamic properties.

1.4. Solid Dispersion: [7]

The term solid dispersion refers to a group of solid products consisting of at least 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 (clusters) or in crystalline particles. In the Biopharmaceutical Classification System (BCS) drugs with low aqueous

solubility and high membrane permeability are categorized as Class II drugs. Therefore, solid dispersion technologiesare particularly promising for improving the oral absorption and bioavailability of BCSClass II drugs.

Table 1.2 BCS Classification System

Class	Solubility	Permeability	Example of drugs
Class I	High solubility	High permeability	Benzapril, Loxoprofen, Sumatriptan etc.
Class II	High solubility	Low permeability	Valsartan, Nimesulide, Loratadine,Aceclofenac, Glimepiride meloxicam etc.
Class III	Low solubility	High permeability	Gabapentine, Topiramate,Atropine etc.
Class IV	Low solubility	Low permeability	Hydrochlorthiazide, Furosemide

Table 1.3. Materials Used as Carrier for Solid Dispersion Technique

Sr. No.	Materials Used asCarriers	Examples
1.	Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, xylitol mannitol ,lactose
2.	Acids	Citric acid, succinic acid
3.	Polymeric Materials	Povidone (PVP), polyethylene glycol (PEG), hydroxypropyl methyl cellulose, methyl cellulose, hydroxy ethyl cellulose, cyclodextrin, hydroxy propyl cellulose, pectin, Galactomannan
4.	Insoluble or enteric polymer	HPMC phthalate, eudragit L100, eudragit S100, Eudragit RL, Eudragit RS
5.	Surfactants	Polyoxyethylene stearate, renex, poloxamer 188, texafor AIP, deoxycholic acid, tweens, spans
6.	Miscellaneous	Pentaerythritol, pentaerythrityl tetraacetate, urea, urethane, hydroxy alkyl xanthins

1.4.1. Types of Solid Dispersions Technique [7]

Chiou and Reigalman classified solid dispersion as follows

1. Simple eutectic mixtures

2. Solid solutions
3. Glass solution and suspension
4. Amorphous precipitation in a crystalline carrier

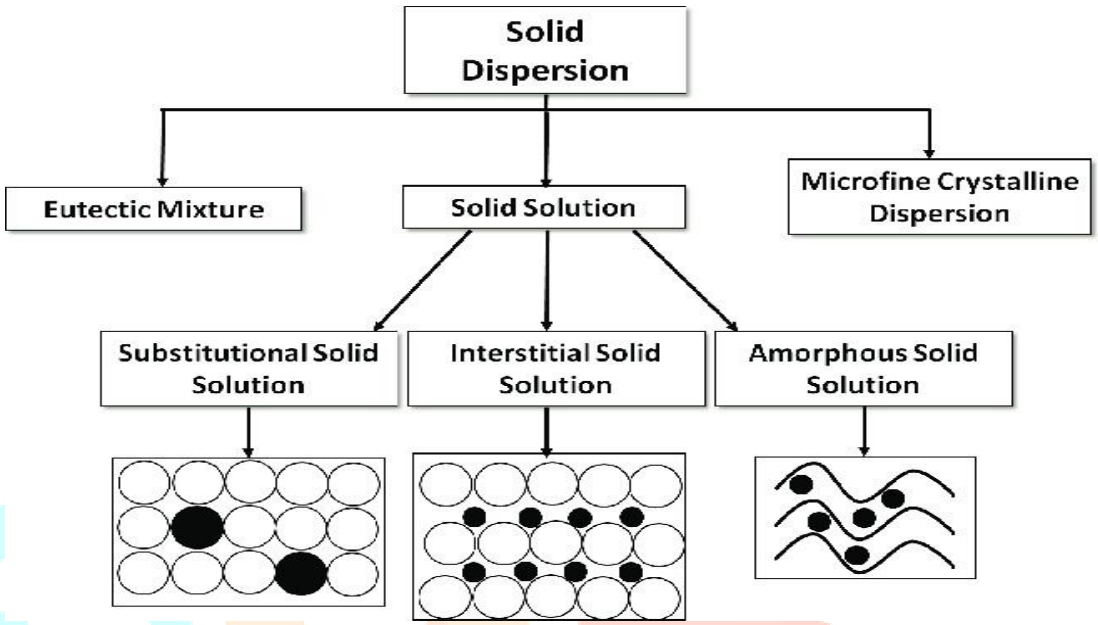


Figure 1.3. Types of Solid Dispersion Technique

1. Simple Eutectic Mixture [41,43]

These are prepared by rapid solidification of the fused melt of two components that show complete liquid miscibility and negligible solid solubility. Thermodynamically,such a system is an intimately blended physical mixture of its two crystalline components. Thus the X-ray diffraction pattern of a eutectic constitutes an additive composite of two components. Ex. Chloramphenicol-urea; Paracetamol-urea.

2. Solid Solution

In a solid solution the two components crystallize together in a homogeneous one phase system. The particle size of the drug in the solid solution is reduced to its molecular size. Thus, a solid solution can achieve a faster dissolution rate than the corresponding eutectic mixture. Solid solutions can be classified by two methods. According to the extent of miscibility of the two components, they may be classified as continuous or discontinuous.

Continuous solid solutions

The two components are miscible in the solid state in all proportions. **Discontinuous Solid Solutions** in the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical phase diagram, show theregions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Below a certain temperature, the mutual solubilities of the two components start to decrease.

Substitutional crystalline solutions

A substitutional crystalline solid dispersion is a type of solid solutions which have a crystalline structure, in which the solute molecules substitute for solvent molecules inthe crystal lattice. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules.

Interstitial crystalline solid solutions

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. In the case of interstitial crystallinesolid solutions, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter. Furthermore, the volume of thesolute molecules should be less than 20% of the solvent.

3. Amorphous Precipitations in a Crystalline Carrier

The difference between this group of solid dispersions and the simple eutectic mixture is that the drug is precipitated out in an amorphous form in the former as opposed to acrystalline form in the latter. E.g. Sulfathiazole was precipitated in the amorphous formin crystalline urea.

Amorphous solid solutions

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using griseofulvin in citric acid, Chiou andRiegelman were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers urea and sugars such as sucrose,dextrose and lactose, organic polymers such as polyvinylpyrolidone (PVP), polyethylene glycol and various cellulose derivatives have been utilized for this purpose.

4. Glass Solution and Suspensions

Glass solutions are homogeneous glassy system in which solute dissolves in glass carrier. Glass suspensions are mixture in which precipitated particles are suspended inglass solvent. Lattice energy is much lower in glass solution and suspension. DifferentCharacteristics of glassy state are transparency, brittleness below the glass transition temperature. e.g., Carriers for glass solution and suspension – citric acid, sugars (dextrose, sucrose, galactose), PVP, PEG, urea.

1.4.2.Methods of Preparation of Solid Dispersion Technique: [45-49]

1. Melting method:

The melting or fusion method, first proposed by Sekiguchi and Obi 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 meltin 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 byquenching the melt

rapidly from a high temperature. Under such conditions, the solutemolecule 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.

2. Solvent method:

In this method, the physical mixture of the drug and carrier is dissolved in a commonsolvent, 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 solvents37.

However, some disadvantages are associated with this method such as

- The higher cost of preparation.
- The difficulty in completely removing liquid solvent.
- The possible adverse effect of traces of the solvent on the chemical stability
- The selection of a common volatile solvent.
- The difficulty of reproducing crystal form.
- In addition, a super saturation of the solute in the solid system cannot beattained except in a system showing highly viscous properties.

3. Melting solvent method (melt evaporation):

It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 –10% (w/w) of liquid compounds can be incorporated into polyethylene glycol6000 without significant loss of its solid property[37]. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporationmethods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg.

4. Melt extrusion method:

The drug/carrier mix is typically processed with a twin-screw extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shapedas tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets.

An important advantage of the hotmelt extrusion method is that the drug/carrier mix isonly subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermolabile to be processed. Solid dispersion by this method iscomposed of active ingredient and carrier, and prepare by hot-stage extrusion using aco rotating twin-screw extruder.

The concentration of drug in the dispersions is always 40% (w/w). The screw-configuration consist of two mixing zones and three transport zones distribute over the

entire barrel length, the feeding rate is fix at 1 kg/h and the screw rate is set at 300rpm.The five temperature zones are set at 100, 130, 170, 180, and 185C from feeder to die.The extrudates are collect after cooling at ambient temperature on a conveyer belt.

5. Lyophilization technique:

Freeze-drying involves transfer of heat and mass to and from the product under preparation[37. 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.

6. Melt agglomeration process:

This technique has been used to prepare SD 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 sprayinga dispersion of drug in molten binder on the heated excipient (spray-on procedure) byusing a high shear mixer. A rotary processor has been shown to be alternative equipment for melt agglomeration. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates. The effect of binder type, method of manufacturing and particle size are critical parameters in preparationof SD(s) by melt agglomeration. Since these parameters result in variations in dissolution rates, mechanism of agglomerate formation and growth, agglomerate size,agglomerate size distribution and densification of agglomerates.

It has been investigated that the melt in procedure gives a higher dissolution rates thanthe 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. Larger particles result in densification of agglomerates while fine particle cause complete adhesion to the mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles.

7. The use of surfactant:

The utility of the surfactant systems in solubilization is well known. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and otherkey properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glasstransition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties,

surfactants have attracted the attentionof investigators for preparation of solid dispersions.

8. Super critical fluid (SCF) technology:

This technology has been introduced in the late 1980s and early 1990s, and experimental proofs of concept are abundant in the scientific literature for a plethora of model compounds from very different areas such as drugs and pharmaceutical compounds, polymers and biopolymers, explosives and energy materials, superconductors and catalyst precursor's dyes and biomolecules such as proteins and peptides. From the very beginning of supercritical fluid particle generation research, the formation of biocompatible polymer and drug-loaded biopolymer micro-particles for pharmaceutical applications has been studied intensively by a number of researchergroups CFs either as solvent: rapid expansion from supercritical solution (RESS) or antisolvent: gas antisolvent (GAS), supercritical antisolvent (SAS), solution enhanced dispersion by supercritical fluids (SEDS) and/or dispersing fluid: GAS, SEDS, particles from gas-saturated solution (PGSS). Conventional methods,

i.e. Spray drying, solvent evaporation and hot melt method often result in low yield, high residual solvent content or thermal degradation of the active substance the supercriticalfluid antisolvent techniques, carbon dioxide is used as an antisolvent for the solute butas a solvent with respect to the organic solvent. Different acronyms were used by various authors to denote micronization processes: aerosol solvent extraction system (ASES), precipitation with a compressed fluid antisolvent (PCA), gas anti-solvent (GAS), solution enhanced dispersion by supercritical fluids (SEDS) and supercritical

anti-solvent (SAS).

The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing concurrently use of supercritical carbon dioxide is advantageous as it is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon dioxide remains trapped inside the polymer; it poses no danger to the patient. In addition, the ability of carbon dioxide to plasticize and swell polymers can also be exploited and the process can be carried out near room temperature 39^0c Moreover, supercritical fluids are used to lower the temperature of melt dispersion process by reducing the melting temperature of dispersed active agent. The reason for this depression is the solubility of the lighter component (dense gas) in the forming phase (heavier component).

1.4.3. Advantages of Solid Dispersions Technique: [8]

1. In particle size results in high surface area resulting in increased dissolution.
2. Particles with higher porosity are produced and this resulting into increase indissolution rate.
3. Improvement in wettability with carrier which can increase in bioavailability.
4. Reduction Converts drug from crystalline to amorphous form thus improving thedissolution and bioavailability.

5. Increase in solubility of many numbers of water insoluble drugs.

1.4.4. Disadvantages of Solid Dispersions Technique:

1. Major disadvantages of solid dispersion are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate withaging.
2. The crystallization of ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the ritonavir capsule (Norvir) from the market.
3. Some solid dispersion may not lend them to easy handling because of tackiness.
4. Moisture and temperature have more deteriorating effect on solid dispersion.
5. Drawback of solid dispersion is their poor scale-up for the purpose of manufacturing.

1.4.5. Mechanism of Solid Dispersion : [9]

The formulations of solid dispersions result into reduction in particle size, improved wettability and enhancement of the dispensability of the drug, thereby markedly improving the dissolution rate. The suggested mechanism behind this tremendous increase in dissolution rate may include:

1. Partial transformation of crystalline drug to the amorphous state or altering the crystalline morphology
2. Formation of solid solution
3. Formation of complexes
4. Intimate mixing of the drug with hydrophilic excipients
5. Reduction of aggregation and agglomeration
6. Improved wetting of the drug and solubilization of drug by the carrier at the diffusion layer.

1.4.6. Application of Solid Dispersion Technique : [38]

1. To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.
2. To stabilize unstable drugs against hydrolysis, oxidation, recrimination.
3. To reduce side effect of certain drugs.
4. Masking of unpleasant taste and smell of drugs.
5. To increase the solubility of poorly soluble drugs thereby increase the dissolutionrate, absorption and bioavailability..
6. To reduce side effect of certain drugs.
7. Masking of unpleasant taste and smell of drugs.
8. Improvement of drug release from ointment creams and gels.
9. To avoid undesirable incompatibilities.
10. To obtain a homogeneous distribution of a small amount of drug in solid state.
11. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
12. To formulate a fast release primary dose in a sustained released dosage form.

13. To formulate sustained release regimen of soluble drugs by using poorly solubleor in soluble carriers.
14. To reduce presystemic inactivation of drugs like morphine and progesterone.
15. No change in chemical properties of the drug.

1.4.7. Carriers for Solid Dispersion: [42,43]

A. Acids - Citric acid, Tartaric acid, Succinic acid

B. Sugars – Dextrose, sucrose, sorbitol, Maltose, Galactose, Xylitol

C. Polymeric materials – Polyvinylpyrollidone, PEG 4000, PEG 6000, HPMC, CMC,Guargum, Xanthum gum, Sodium alginate, Cyclodextrin.

D. Surfactants – Poloxamer, Tween, Span, Gelucire 44/14, Deoxycholic acid,Polyoxyethelenestearate, Vitamin E TPGS NF.

1.4.8. Ideal Properties of Carrier:

The properties of the carrier have a major influence on the dissolution characteristics of the dispersed drug. A carrier should meet the following criteria to be suitable for increasing the dissolution rate.

a. It should be freely water soluble with intrinsic rapid dissolution properties.
b. It should be non-toxic and pharmacologically inert.
c. It should be heat stable with a low melting point for the melt method.
d. It should be soluble in variety of solvents and pass through a vitreous stateupon solvent evaporation for the solvent method.
e. It should be able to preferably, increase the aqueous solubility of the drug.
f. It should be chemically compatible with the drug and should not form astrongly bonded complex with the drug.

Characterization of Solid Dispersion Technique:[25,28]

Many methods are available that can contribute information regarding the physical nature of solid dispersion system. A combination of two or more methods is required to study its complete picture.

- Thermal analysis.
- Spectroscopic method.
- X-ray diffraction method.
- Dissolution rate method.
- Microscopic method.
- Thermodynamic method.
- Modulated temperature differential scanning calorimetry
- Environmental scanning electron microscopy

- Dissolution testing

Recent Advances and Future Trends: [13]

Solid dispersion has great potential both for increasing the bioavailability of drug anddeveloping controlled release preparations. Thus, to solve bioavailability issues with respect to poorly water- soluble drugs, solid dispersion technology has grown rapidly. Thedosage form can be developed and prepared using small amounts of drugs substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micronization of drugs and soft gelatin encapsulation.

Although there are many superdisintegrants, which show superior disintegration, the searchfor newer disintegrants is ongoing and researchers are experimenting with modified naturalproducts, like formalin casein, chitin, chitosan, polymerized agar acrylamide, xylan,smecta, key jo-clay, crosslinked carboxymethyl guar and modified tapioca starch. Studieshave suggested that the water insoluble superdisintegrants show better disintegration property than the slightly water soluble agents, since they do not have a tendency to swell.Superdisintegrants that tend to swell show slight retardation of the disintegration propertydue to formation of viscous barrier. There is no particular upper limit regarding the amountof superdisintegrant as long as the mechanical properties of the tablet are compatible with its intended use. The superdisintegrant may be used alone or in combination with other superdisintegrants.

2. LITERATURE REVIEW

Extensive literature review was taken from library and from different web portal availableon internet to gain insight into the work done by various researchers to find out the variousparamters and factors that are necessary for the formulation and evaluation of fenofibrate drug like

- Disease and drug information
- Methods of Preparation
- Types of Polymers and Excipients
- Various evaluation paramters and techniques
- List of various authors/Inventors and their work done

1. Nelvia Helsinta, et al (2021) studied that Several research journals above show that for the fenofibrate solid dispersion system using β cyclodextrin, fusion (melting), solvent evaporation, dropping, and co-grinding techniques are often used. It was also found that Beta cyclodextrin had a higher dissolution than other formulations and reduced particle size, increasing the solubility. The greater the speed of melting, the more excellent the solubility of a drug.

2. **Davesh Jire, et al (2021)** studied that the technology described in this article indicatesthat recent developments have taken place development and processing technology meets the efforts to achieve complex drugs delivery system.

3. **Navneet Kumar Verma, et al (2014)** studied that Development and evaluation of solid dispersion of fenofibrate using polyethyleneglycol as carrier, From the studies it is concluded that the formulation with drug: carrier ratio 1:5(PEG4000) showed better dissolution rate in comparison with pure drug.

4. **Harendra Prasad, et al (2014)** studied that In order to improve the solubility and oralabsorption of the drug in gastric fluid and to enhance its dissolution rate solid dispersion evaluated. Solid dispersions of Fenofibrate were prepared using PEG 4000 and Beta cyclodextrin in different ratios by solvent evaporation method from the studies it is concluded that the formulation with drug: carrier ratio 1:5(Beta cyclodextrin) showed better dissolution rate in comparison with pure drug.

5. **R. Bala, et al (2018)** studied that the aforesaid findings indicate that the created formulation has the potential to be a new dosage form for improving medication distribution, start of action, and patient compliance.

6. **Padilla Walkar et al. (2018)** studied that he interaction between drugs and polymers was studied using FTIR spectroscopy. Among all formulations, the formulation (F8) containing 4% crosspovidone had the highest drug release (99.27%) and demonstrated good stability overa three month period.

7. **Ali Raza et al. (2019)** studied that the treatment of hypertension that had quick disintegration, optimal morphological qualities, and mechanical strength. Losartan is an antihypertensive medication that goes through a lot of first-pass metabolism, which meansit has a low bioavailability. The medicine enters the bloodstream immediately through thebuccal route, increasing its bioavailability.

8. **Nelvia Helsinta, et al (2021)** studied that Several research journals above show that for the fenofibrate solid dispersion system using PEG 4000, fusion (melting), solvent evaporation, dropping, and co-grinding techniques are often used. It was also found that PEG 4000 had a higher dissolution than other formulations and reduced particle size, increasing the solubility and dissolution rate. The greater the speed of melting, the more excellent the solubility of a drug.

10. **Ravi. S.K, et al (2021)** studied that the MDFs of Ondansetron formulations containingHPMC and Superdisintegrants Starch showed least disintegration time and In vitro drug release was faster than the other formulation.

11. **Ali Q. Hatem, et al (2022)** studied that solid dispersion using hydrophilic carrier is one of the approach that has potential to increase solubility and oral bioavailability of method. The batches prepared are evaluated for drug content , solubility .The result showed that β-cyclodextrin , PEG 4000 used in solid dispersion improve solubility.

12. **Tiwari shradha, et al (2020)** studied that physical mixing, kneading technique & solvent evaporation methods were used for preparation of solid mixture of drug selected From BCS class II. All the solid mixture were prepared are found to be fine an free flowing powders. Drug carrier interaction studies were carried on the optimized solid mixtures by FTIR.

13. Ritu Kaushik, et al (2018) studied that there are various approaches for preparation of solid dispersion, such as solvent melting, hot melt extrusion method, kneading method etc

14. Sonpal Rakshit N., et al (2017) studied that drug polymer solid dispersion approach have been conceptualized & used where prepared using the Kneading Method. It could be concluded that drug polymer solid dispersion approach is a promising approach which can be utilised for improving bioavailability of poorly soluble drug.

15. Biradar Mahesh, et al (2016) studied that β-cyclodextrin was used in the preparation of solid dispersion by the physical mixture and kneading method. Formulation containing fenofibrate + β-cyclodextrin (1:5) shows better result by kneading method & shows great bioavailability.

16. Ravi wanare, et al (2015) studied that solid dispersion technique is used as effective method to enhance the solubility and bioavailability of poor water soluble drug.

3. NEED OF WORK

- Fenofibrate is hypolipidemic, class II drug so, the major problem of Fenofibrateis its very low solubility in biological fluids so to overcome the problem of lowsolubility, there is need to enhanced solubility of drug by any appropriate method.
- Due to poor aqueous solubility of Fenofibrate makes its absorption and dissolution rate limited, thus delaying onset of action.
- So in this research work solubility of fenofibrate was enhanced to increase the absorption rate of fenofibrate dosage form.

AIM AND OBJECTIVES

AIM: To Enhance the solubility of Fenofibrate by solid dispersion technique.

OBJECTIVES:

- To improve solubility of fenofibrate by using solid dispersion technique.
- Characterization of solid dispersion of fenofibrate.
- To prepare solid dispersion of fenofibrate by using Beta-cyclodextrin.

4. PLAN OF WORK

1. Literature Survey

2. Selection of Drug & Excipients

3. Preformulation Studies of Drug
   - Identification & characterization of Fenofibrate
   - Spectrophotometric analysis of drug
   - Drug-Excipient compatibility

4. Preparation of Solid Dispersion by using Beta cyclodextrin

- Preparation of drug polymer complexes in different ratios by using kneading method.
- Comparative solubility and dissolution study of solid dispersion.

5. Evaluation of Selected Solid Dispersion

- Physical appearance
- Solubility study of solid dispersion
- Fourier transform infrared study of solid dispersion
- Drug content of solid dispersion
- Percentage practical yield of solid dispersion

6.Compilation Data

6. MATERIALS AND EQUIPMENTS

MATERIALS

Table 6.1: List of Materials

Sr. No.	Name of Material	Category	Name of Supplier
1	Fenofibrate	API	Mylan Laboratories Limited, Sinnar.
2	β-cyclodextrin	Polymer	Research lab fine chemical Industry, Mumbai.
3	Methanol	Solvent	Research lab fine chemical Industry, Mumbai.

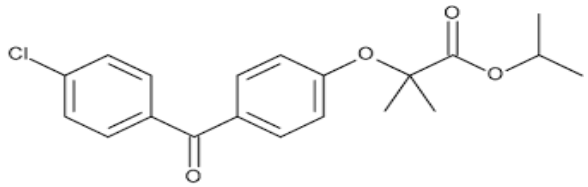
EQUIPMENTS

Table 6.2: List of Equipments

Sr. No.	Name of Equipments	Supplier Company Name
1	Electronic Balance	Shimadzu, Japan(Model AUY220)
2	pH Meter	Lab India, Mumbai (Model GMPH)
3	UV- Spectrophotometer	Jasco, Japan(Model : V-730ST)
4	Hot Air Oven	Remi, Mumbai (Model:5MLH DX)
5	FT-IR Spectrophotometer	Jasco, Japan.(Model FTIR-8400S)
6	Melting Point Apparatus	Veego, Mumbai (PMP-D)

7. DRUG PROFILE

Table 7.1 Drug Profile of Fenofibrate

Name	Fenofibrate
Category	Hypolipidemic
CAS registry number	49562-28-9
Chemical structure	
Chemical formula	$C_{20}H_{21}ClO$
IUPAC name	propan-2-yl 2-[4-(4-chlorobenzoyl) phenoxy]-2-methylpropano
BCS Class	Class-II
Molecular weight	360.831
Apperance, Colour, Odour	White Crystalline Powder
Dose	50-130mg per day
Melting Point	79°C to 82°C
Solubility	Soluble in Organic Acids Insoluble in Water
Storage	Stored in a cool place away from light and moisture
Pka(strongest Basic)	-4.9

Half Life	20hrs
Protein Binding	Fenofibrate is 99% protein bound in serum, primarilyto albumin
Log P	5.28
λ Max	280nm
Cmax	6-9.5mg/l

Bioavailability	60%
Absorption	A single 300mg oral dose of Fenofibrate reaches a C_{max} of 6-9.5mg/l with a T_{max} of 4-6h in healthy,fasting volunteers
Volume of Distribution	The volume of distribution of Fenofibrate is 0.89L/kg,and can be as high as 60L
Metabolism	Fenofibrate is completely hydrolyzed by liver carboxyl esterase 1 to fenofibric acid. Fenofibric acid is either glucuronidated or has its carbonyl group reduced to a benzhydrol that is then glucuronidated. Glucuronidation of Fenofibrate metabolites is mediated by UGT1A9.Reduction of the carbonyl group is primarily mediated by CBR1 and minorly byAKR1C1, AKR1C2, AKR1C3, and AKR1B1.
Route of Elimination	5-25% of a dose of Fenofibrate is eliminated in the feces, while 60-88% is eliminated in the urine.70-75%of the dose recovered in the urine is in the form of fenofibryl glucuronide and 16% as fenofibric acid.

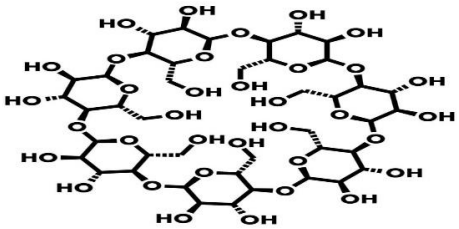
Mechanism of action	Fenofibrate activates peroxisome proliferator activated receptor alpha (PPARα), increasing lipolysis, activating lipoprotein lipase, and reducing apoprotein C-III. PPARα is a nuclear receptor and its activation alters lipid, glucose, and amino acid homeostasis. Activation of PPARα activates transcription of gene transcription and translation thatgenerates peroxisomes filled with hydrogen peroxide,reactive oxygen species, and hydroxyl radicals that also participate in lipolysis. This mechanism of increased lipid metabolism is also associated with
	increased oxidative stress on the liver. In rare casesthis stress can lead to cirrhosis and chronic active hepatitis.
Clearance	The oral clearance of Fenofibrate is 1.1L/h in young adults and 1.2L/h in the elderly.
Pharmacodynamics	Fenofibrate is a fibrate that activates peroxisome proliferator activated receptor alpha (PPARα) to alter lipid metabolism and treat primary hypercholesterolemia, mixed dyslipidemia, and severehypertriglyceridemia. Fenofibrate requires once daily dosing and has a half life of 19-27 hours so its duration of action is long. Fenofibrate capsules are given at a dose of 50-150mg daily so the therapeutic index is wide. Patients should be counselled about therisk of rhabdomyolysis, myopathy, and cholelithiasis when taking fibrates.

Adverse Effects	**The more common side effects that can occur withuse of Fenofibrate include:** Headache Back pain Nausea Indigestion Stuffy or runny nose Stomach pain
Uses	Fenofibrate is used together with a proper diet **to reduce and treat high cholesterol and triglyceride(fat-like substances) levels in the blood**. This may help to prevent the development of pancreatitis (inflammation or swelling of the pancreas) caused byhigh levels of triglycerides in the blood

Dosage forms	Tablets, Chewable tablets
Brand Names	*Antara, Cholib, Fenoglide, Fenomax, Lipidil Supra, Lipofen, Tricor, Triglide.*

7. EXCIPIENT PROFILE [29-31]

Table 8.1 : Beta Cyclodextrin

Non proprietry names	Beta Cyclodextrin
Synonyms	Cycloheptaamylose, Cycloheptadextrin, Beta cycloamylose, Schardinagar Beta -Dextrin.
Structure	
Chemical name	(2-O-α-D-Glucopyranosyl)-β-D-glucopyranose.
CAS Registry Number	7758-39-9

Molecular Formula	$C_{42}H_{70}O_{35}$
Molecular Weight	1134.987 g/mol
Melting Point	290-300ºC
Description	Beta cyclodextrin is a cyclic oligosaccharides consisting of seven glucose unit joined by for glycosidic bond ,compound used to modify therapeutic protein and peptides to increase their solubility.
Storage & Stability	Store in a dry place. Protect from moisture.

Application	Beta cyclodextrin provides enhance solvency, lubricity, hygroscopicity, solubilizer.

9.EXPERIMENTAL WORK

9.1.Preformulation Studies of Fenofibrate

9.1.1.Identification and Characterization of Fenofibrate

1. Organoleptic evaluation

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

2. Melting point

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

3. Solubility profile

Solubility determination can be done by ultraviolet absorption, nephalometry, Nuclearmagnetic resonance and Potentiometric in drug discovery. A drug is considered highlysoluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1 to 7.5. The volume estimate of 250 ml is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fastinghuman volunteers with a glass of water.

4. Loss on drying

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

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

9.2.UV spectroscopic Analysis of Fenofibrate

9.2.1. Scanning of Fenofibrate in Phosphate Buffer pH 6.8 Solution

The standard solution (10µg/ml℃) was scanned from 200-400 nm on UV spectrophotometer (Shimadzu UV–1800). The absorption maxima were found to be at280 nm in phosphate buffer pH 6.8.

9.2.2. Preparation of Phosphate Buffer pH 6.8

The phosphate buffer pH 6.8 was prepared by mixing the 28.20 gm of disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen in sufficient distilled water

to produce 1000ml.

9.2.3. Procedure

An accurately weighed quantity of Fenofibrate was transferred into a 50 ml volumetricflask, diluted up to the mark with phosphate buffer pH 6.8 to get a standard stock solution of 0.5 mg/ml. Aliquot portions of standard stock solution was appropriately diluted to get the concentration of 10µg/ml and scanned in the range 400-200 nm. Thezero order spectrum and its first order derivative spectrum were recorded. The calibration curve is shown in figure 10.2. Absorbances of different concentration of Fenofibrate are reported in table 10.4.

9.3.Drug Excipient Compatibility Studies

9.3.1. FTIR Spectroscopy of Fenofibrate, Fenofirate and Beta cyclodextrin

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

9.4.Formulation and Development

9.4.1. Preparation of Solid Dispersion

Solid dispersion of drug and polymer was prepared by using solvent kneading method with the help of Beta cyclodextrin in various ratios.

Kneading Method

In this method, preparation of solid dispersions Fenofibrate with all carriers took place.The ratio of drug and carriers were1: 1, 1: 2, 1: 3, 1:4 and 1:5. The drug and the carrierswere kneaded in water for a particular time to form thick paste. Afterwards it was dried in Hot Air Oven at 60℃ for 1 hour.

The product samples were pulverized using a glass mortar and pestle, sieved through 60 meshes and kept the powder of solid dispersion in desiccators throughout the experimental period. The ratio of drug and

carriers were shown in table no.9.1.

Table 9.1. Formulation of Drug and Polymer

Formulation /Batches	Composition	Method	Ratio
F1	Fenofibrate + β-cyclodextrin	Kneading Method	1:1
F2	Fenofibrate + β-cyclodextrin	Kneading Method	1:2
F3	Fenofibrate + β-cyclodextrin	Kneading Method	1:3
F4	Fenofibrate +β-cyclodextrin	Kneading Method	1:4
F5	Fenofibrate +β-cyclodextrin	Kneading Method	1:5

9.5.Comparative Solubility Study of solid dispersion technique

9.5.1. Solubility study of solid dispersion and Fenofibrate

Solubility measurement of Fenofibrate were performed according to published method.The amount of solid dispersion powder containing 2.5 mg equivalents Fenofibrate wasweighed accurately, but taken in excess amount. It is then taken in volumetric flask and dissolved in distilled water by sonication for 15min, the solutions were filtered through a Whatmann filter paper no.1. Filtered solution was diluted properly with distilled water. The diluted solution was analysed for Fenofibrate in UV at 280 nm.

9.6.Evaluation of Solid Dispersion Technique

9.6.1Physical Appearance

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

9.6.2Percentage Yield Study of Solid Dispersion

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

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

Where,

a = Practical weight of solid dispersion obtained

b = Theoretical weight of solid dispersion prepared

9.6.3Drug Content

Drug content analysis was done by preparing 1 µg/ml solution of the solid dispersion Samples in methanol. Samples equivalent to 50 mg fenofibrate was dissolved in 50 ml of methanol. This solution was kept for 24 h for complete extraction of the 4 hrs ,of the drug. After 24 hrs , the solution was filtered and a 50 ug/ml solution was prepared with this solution by dilution with methanol. The solution was assayed through UV spectrophotometric method.

% drug content =X/Y ×100

X= concentration obtained from spectrophotometer analysis.

Y= Theorotical concentration.

10. RESULT AND DISCUSSION

10.1. Preformulation Studies of Fenofibrate

10.1.1. Identification and characterization of Fenofibrate

1. Organoleptic Properties

Organoleptic evaluation reveals that the sample of Fenofibrate obtained was compliedwith standards. The result is presented in the table 10.1.

Table 10.1 : Identification tests of Fenofibrate with the reported standards.

Sr.No.	Identification Test	Observation	Inference

1.	Appearance	Fine powder	Complies with IP
2.	Colour	White	Complies with IP
3.	Odour	Odourless	Complies with IP

2. Melting Point

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

3. Solubility Study of Drug

The descriptive form of solubility profile according to parts of solvent required for 1parts of solute given in the table 10.2.

Table 10.2 : Solubility study of Fenofibrate in the different solvents

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

4.Loss on Drying

The percentage loss on drying after 4hours was found to be 0.3%. The sample passestest for loss on drying as per the limits specified in I.P. (N.M.T 0.4%) given in table 10.3.

10.3: Percentage loss on drying of Fenofibrate

Sr. No.	Percentage LOD	Average Percentage LOD
1	0.2	0.3±0.1
2	0.4	
3	0.3	

10.2. UV SPECTROSCOPIC ANALYSIS OF FENOFIBRATE

10.2.1. Scanning of Fenofibrate in Phosphate Buffer 6.8 Solution

The standard solution of Fenofibrate in Phosphate buffer 6.8 was scanned in the rangeof 200-400nm and absorbance maxima was found at 280nm. The result is shown in figure 10.1.

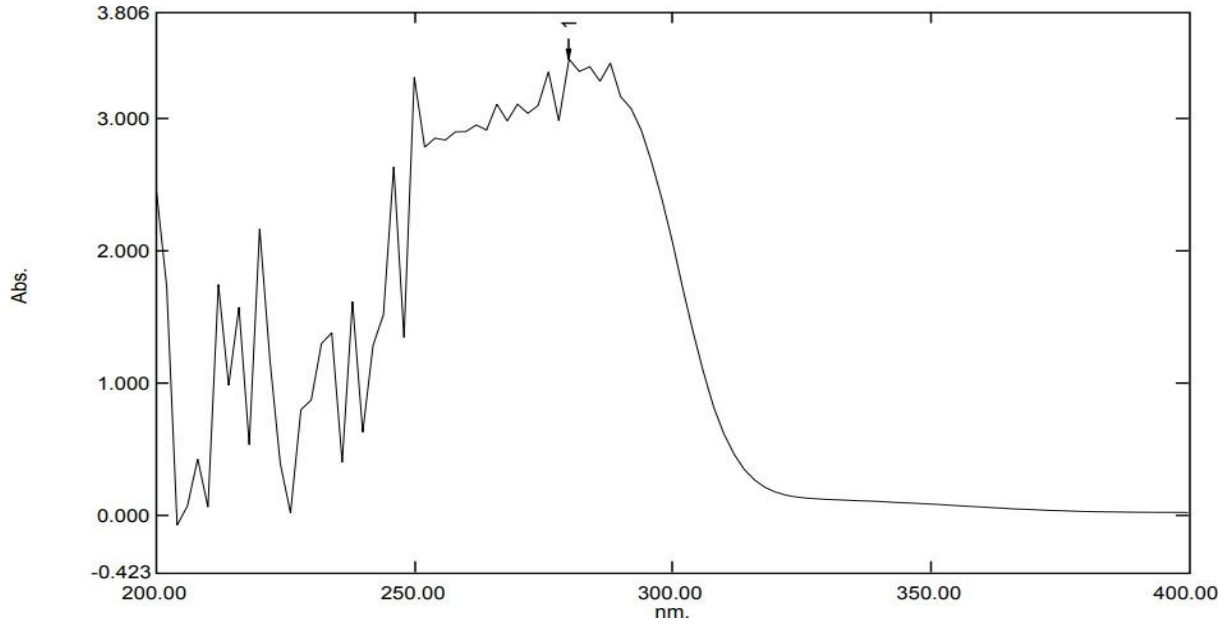


Figure 10.1. UV spectra of Fenofibrate in phosphate buffer 6.8Standard calibration curve of Fenofibrate in phosphate buffer 6.8

The calibration curve was constructed by plotting concentration vs. absorbance of fenofibrate from above readings. The drug was found to obey Beer's Law. The R^2 value was found to be 0.9993. absorbance value were depicted in table 10.4.

Table 10.4: Calibration curve of Fenofibrate in phosphate buffer 6.8

Sr. No.	Concentration (µg/ml)	Absorbance
1	10	0.039
2	20	0.058
3	30	0.085
4	40	0.12
5	50	0.149

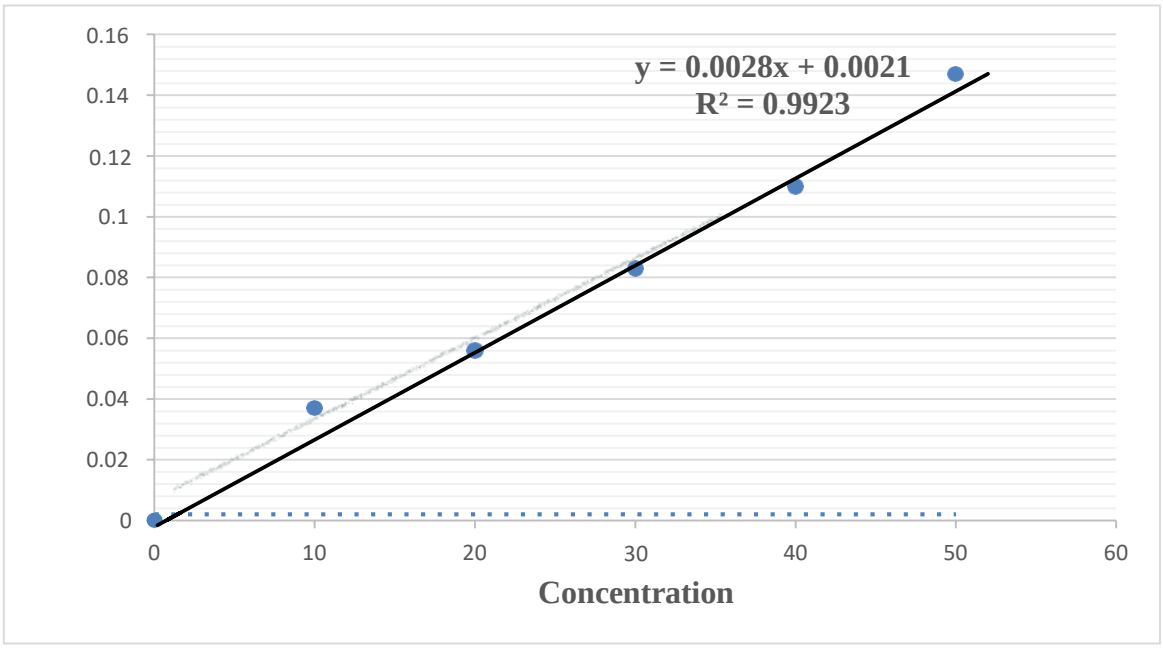


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Figure 10.2: Standard graph of Fenofibrate in phosphate buffer 6.8

10.2.2 Scanning of Fenofibrate in Distilled Water

The standard solution of Fenofibrate in Distilled Water was scanned in the range of 200-400nm and absorbance maxima was found at 280nm. The result is shown in figure 10.2..

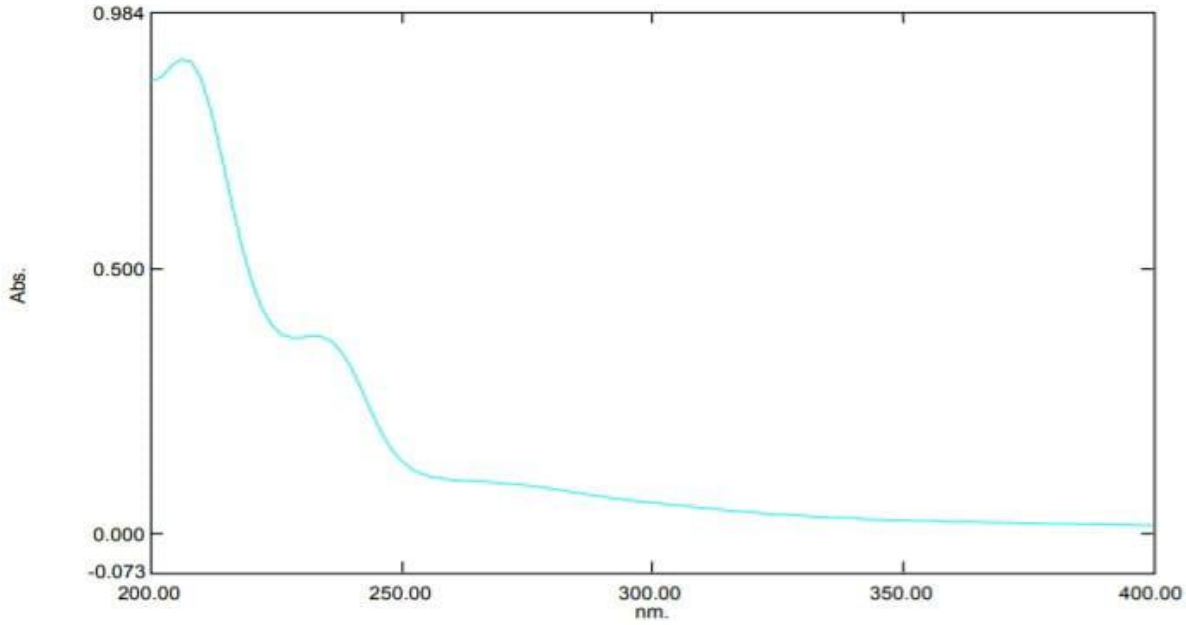

Figure 10.3 : UV Spectra of Fenofibrate in Distilled water.

Standard calibration curve of Fenofibrate in Distilled Water.

The calibration curve was constructed by plotting concentration vs. absorbance of fenofibrate from above readings. The drug was found to obey Beer's Law. The R^2 value

Was found to be 0.9991. Absorbance value were depicted in table 10.5.

Table 10.5: Calibration Curve of Fenofibrate in Distilled Water

Sr. No.	Concentration (µg/ml)	Absorbance
1	10	0.013
2	20	0.025
3	30	0.035
4	40	0.046
5	50	0.060

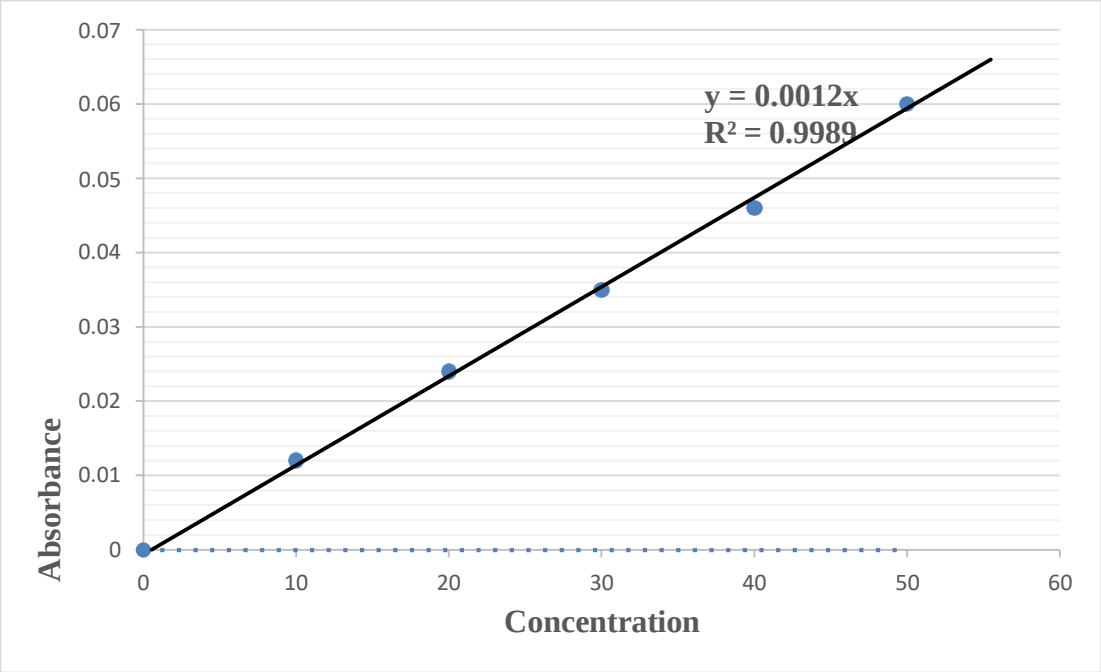

Figure 10.4: Standard graph of Fenofibrate in distilled water.

10.2.2 Scanning of Fenofibrate in Methanol.

The standard solution of Fenofibrate in Methanol. was scanned in the rangeof 200-400nm and absorbance maxima was found at 285nm. The result is shown in figure 10.5.

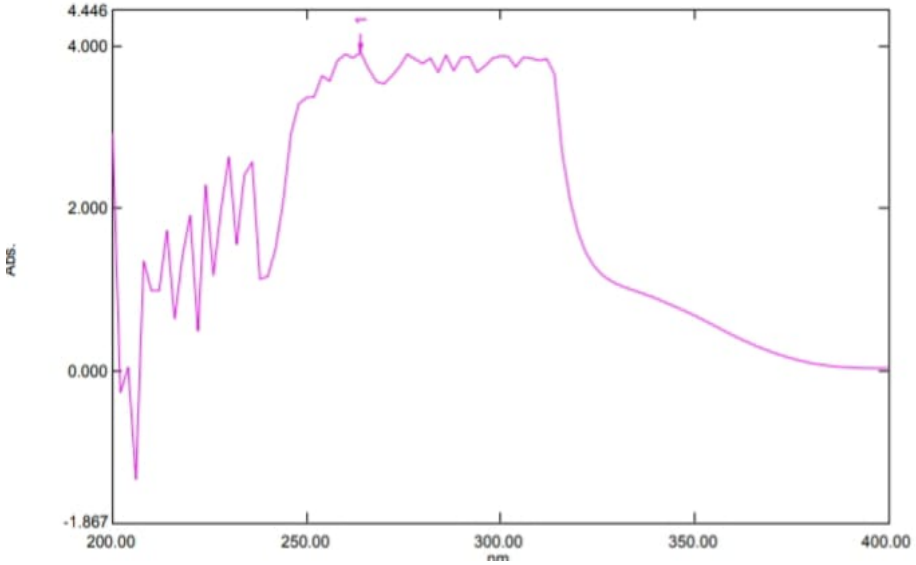

Figure 10.5: UV Spectra of Fenofibrate in Methanol.

Standard calibration curve of Fenofibrate in Distilled Water.

The calibration curve was constructed by plotting concentration vs. absorbance of fenofibrate from above readings. The drug was found to obey Beer's Law. The R^2 value

Was found to be 0.9902. Absorbance value were depicted in table 10.6.

Table 10.6: Calibration Curve of Fenofibrate in Distilled Water

Sr. No.	Concentration (µg/ml)	Absorbance
1	10	0.039
2	20	0.058
3	30	0.085
4	40	0.12
5	50	0.149

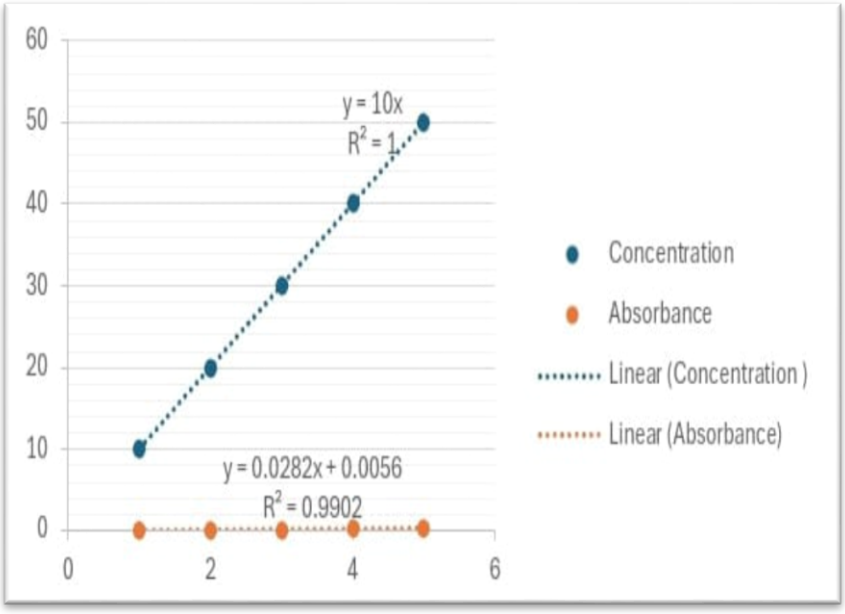

Figure 10.6 : Standard graph of Fenofibrate in Methanol.

10.3.DRUG EXCIPIENT COMPATIBILITY STUDIES

10.2.2. Fourier Transform Infra Red Spectroscopy of Fenofibrate

IR spectra of Fenofibrate and its physical mixture with formulation excipients were determined using FT-IR. Pure Fenofibrate spectra showed sharp characteristic peaks at1725.25, 2361.90 and 3700.5cm^{-1}. FTIR-spectra of Fenofibrate and its physical mixture with excipients are exactly same, and there is no shift of peaks or disappearance of principle peaks or modification of the principle peaks indicating that there is no interaction between the drug and excipients.

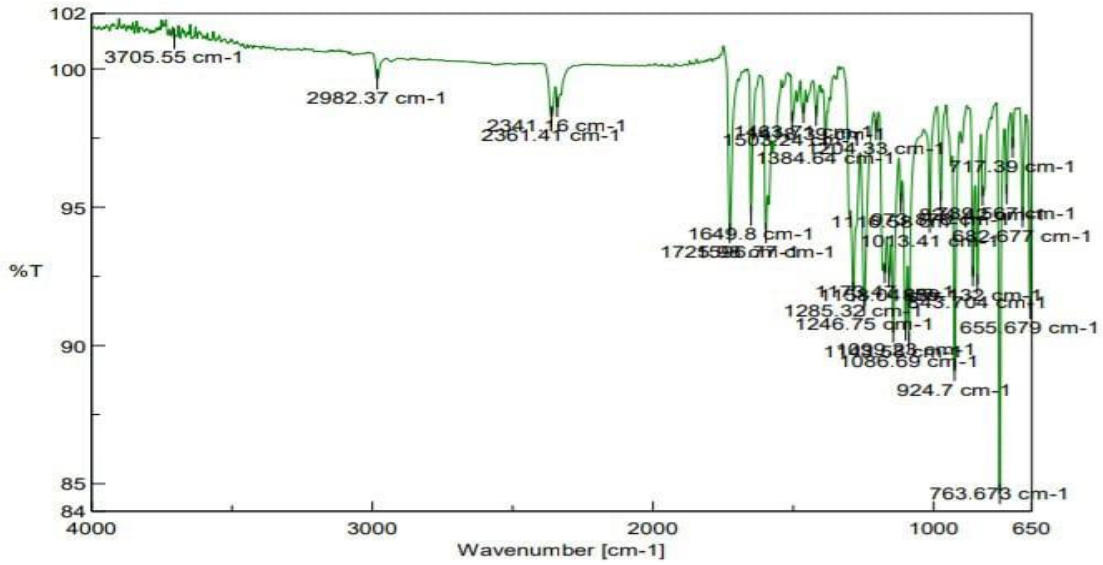

Figure 10.7: FTIR spectra of Fenofibrate.

Table 10.7: FTIR peaks of Fenofibrate

Reference Peak Wavenumber (cm^{-1})	Observed Peak Wavenumber (cm^{-1})	Functional Group
1705-1740	1725.25	C=O Stretch
2300-2500	2361.16	C-H Stretch
3500-3800	3700.5	O-H Stretch

10.3.2:Fourier Transform Infra Red Spectroscopy of Fenofibrate + Beta Cyclodextrin

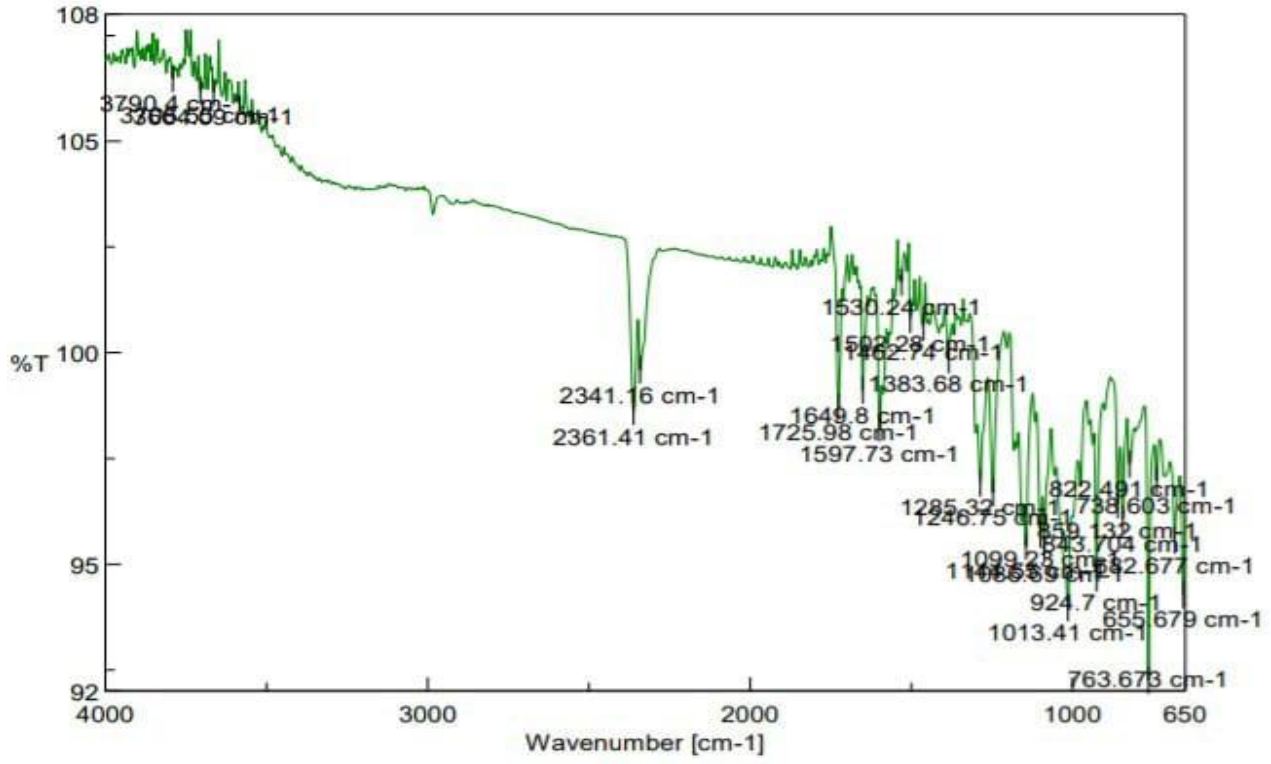

Figure 10.8: FTIR spectra of Fenofibrate + Beta Cyclodextrin

Table 10.8: FTIR peaks of Fenofibrate + Beta Cyclodextrin

Reference Peak Wavenumber (cm^{-1})	Observed Peak Wavenumber (cm^{-1})	Functional Group
1705-1740	1725.98	C=O Stretch
2300-2500	2361.41	C-H Stretch
3500-3800	3790.90	O-H Stretch

10.3. FORMULATION AND DEVELOPMENT

10.3.1. PREPARATION OF FENOFIBRATE SOLID DISPERSION

The formulation of solid dispersion prepared by Kneading technique by using polymer like Beta cyclodextrin respectively in various ratios such as Fenofibrate and beta cyclodextrin (1:1, 1:2, 1:3, 1:4, 1:5). Solid dispersions prepared by using Beta cyclodextrin were F1, F2, F3, F4,F5 .

10.4. Comparative Solubility Study.

10.4.1. Solubility of Solid Dispersion

Table 10.9. Solubility study of Solid Dispersion and Fenofibrate

Formulations	Drug : Carrier	Solubility(mg/ml)
Pure Drug	Pure Drug	0.003±0.001
F1	Fenofibrate +Beta cyclodextrin(1:1)	60.80±0.02
F2	Fenofibrate +Beta cyclodextrin (1:2)	65.96±0.12
F3	Fenofibrate +Beta cyclodextrin (1:3)	72.50±0.06
F4	Fenofibrate +Beta cyclodextrin(1:4)	80.76±0.09
F5	Fenofibrate +Beta cyclodextrin(1:5)	89.54±0.03

Solubility study of various solid dispersion trial batches was performed. Solid dispersion

Prepared by using Beta Cyclodextrin improved solubility of fenofibrate as compared to pure drug,

The batch F5 was more soluble than pure drug and other formulation batches .

10.5. Evaluation Solid Dispersion

The solid dispersion of Fenofibrate were evaluated for number of parameters like physical appearance, % practical yield, solubility study, % drug release and compatibility study**.**

1.Physical Appearance All batches of solid dispersion were evaluated for color and appearance. The physical appearance of each formulation is shown in table 10.10.

10.10: Physical Appearance of formulations Drug and Polymer

Sr.No.	Formulation	Color	Appearance
1	**F1**	Off White	Powder
2	**F2**	Off White	Powder
3	**F3**	Off White	Powder
4	**F4**	Off White	Powder
5	**F5**	Off White	Powder

2.**Percentage Practical Yield of Solid Dispersion**

Percentage practical yield was calculated to know about % yield or efficiency of any polymer which will help in selection of appropriate method. The practical yield of eachbatch is reported in table 10.11.

Table 10.11: Practical yield of solid dispersion

Formulation	Initial weight (mg)	Final weight (mg)	% PracticalYield
F1	2000	1901	95.05±0.001
F2	3000	2889	96.30±0.012
F3	4000	3893	97.32±0.06
F4	5000	4853	97.06±0.09
F5	6000	5799	96.65±0.03

(Drug is taken in 1000 mg)

Different trial batches of solid dispersion show % practical yield range from 95.05 to 96.65. Batch F5 showed 96.65% practical yield.

1. Drug Content of Solid Dispersion of Optimized Formulation F5

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

2.Characterization of Solid Dispersion

Fourier transform infra red spectroscopy (FTIR) interpretation

Major functional groups present in Fenofibrate show characteristic peaks in IR spectrum. Table 10.12 and table 10.1 shows peaks observed at different wave numbersand the functional group associated with these peaks. The major peaks are identical to functional group of Fenofibrate. Hence, the sample was confirmed as Fenofibrate.

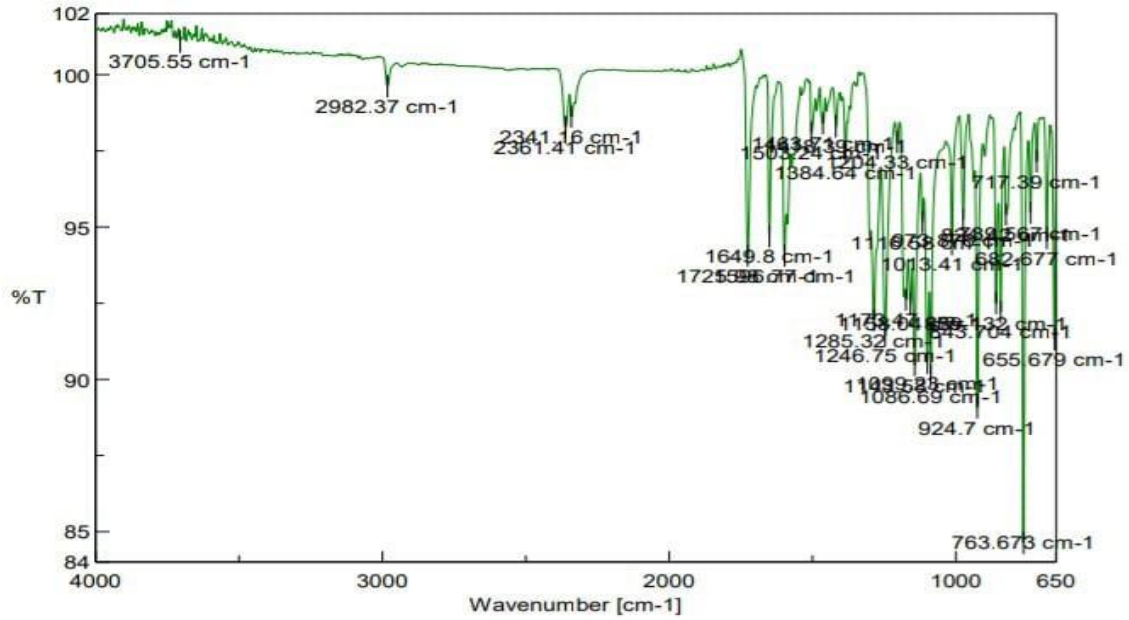

Figure 10.9: FTIR spectra of Fenofibrate

Table 10.12: FTIR peaks of Fenofibrate

Reference Peak Wavenumber (cm^{-1})	**Observed Peak Wavenumber (cm^{-1})**	**Functional Group**
1705-1740	1725.25	C=O Stretch
2300-2500	2361.16	C-H Stretch
3500-3800	3700.41	O-H Stretch

FTIR Studies of Solid Dispersion

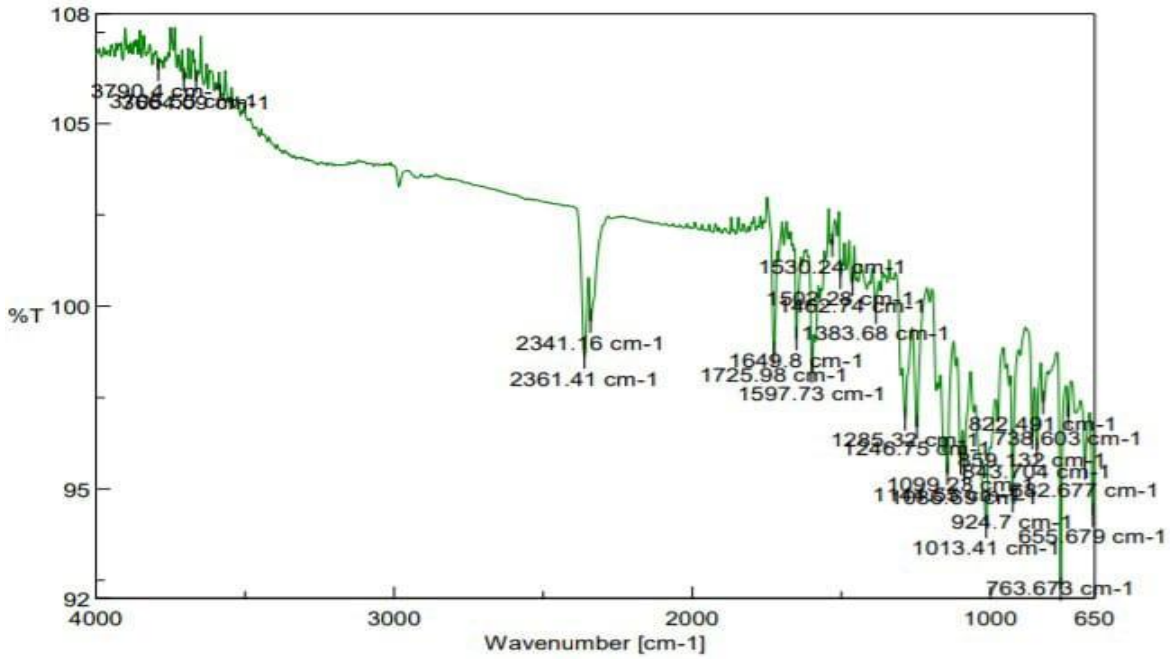

Figure 10.10: FTIR spectra of solid dispersion

Table 10.13: FTIR peaks of solid dispersion

Reference Peak Wavenumber (cm^{-1})	Observed Peak Wavenumber (cm^{-1})	Functional Group
1705-1740	1725.25	C=O Stretch
2300-2500	2361.41	C-H Stretch
3530-3800	3790.41	O-H Stretch

The spectrum of pure drug and solid dispersion is showed in figure 10.7 and 10.10

In above IR spectra the peak of drug and polymer are shown in table 10.12 and 10.13.

All these peaks are appeared in formulation and physical mixture indicating no chemical interaction between fenofibrate and polymer.

11. SUMMARY AND CONCLUSION

SUMMARY

- Fenofibrate is an Hypolipidemic Drug.

- In present study, the attempts have been made to increase the dissolution of BCS class II drug Fenofibrate using hydrophilic polymer Beta cyclodextrin by Kneading Method of solid dispersion. Drug polymer complex were prepared. Total five formulations of solid dispersion were prepared. The solid dispersion of Fenofibrate were evaluated for parameters like physical appearance, percentage practical yield, solubility study, drug content and drug-excipient compatibility study(FTIR).
- The physical appearance of all F1 to F5 formulations was white fine powder,Solubility study results between 60.80 to 89.54 mg/ml and drug content of F5 formulation was found to be 99.25%.
- The results obtained in FTIR study clearly indicate that there was no interaction found between drug and excipients.

CONCLUSION

- All the formulations of solid dispersions of Fenofibrate were successfully preparedand evaluated for solubility.
- The saturation solubility of drug was found to be more in the solid dispersions as compared to pure drug.
- From FTIR spectroscopy studies, it was concluded that there was no defined chemical interactions between Fenofibrate and Beta cyclodextrin. It can provide a promising way to enhance its solubility and dissolution rate of poorly soluble drug.

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