ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF FENOFIBRATE BY USING LIQUISOLID TECHNIQUE

By: Navneet Batra & Avadhesh Kumar Mishra

PROMOTED BY: ASSOCIATION FOR INNOVATION

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CHAPTER-1
INTRODUCTION

Liquisolid technique is a new approach for delivery of drugs through oral route. This technique is suitable for poorly or water insoluble drugs, highly permeable drugs ((BCS Class II drugs) and also for immediate or sustained release formulations. Design of this technique was according to new mathematical model proposed by Spireas *et al*. Liquisolid technique as a tool for enhancement of poorly water-soluble drugs and evaluation of their physicochemical properties.[1]

Liquisolid technique has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. The dissolution properties of a drug and its release from a dosage form have a basic impact on its bioavailability. Solving solubility problems is a major challenge for the pharmaceutical industry with developments of new pharmaceutical products. There are various methods but liquisolid technique is a new and promising method that can change the dissolution rate of water insoluble drugs.[2]

There are various methods to enhance drug solubility but liquisolid technique is one of the promising technique The dissolution properties of a drug and its release from a dosage form have a basic impact on its bioavailability. Solving solubility problems is a major challenge for the pharmaceutical industry with developments of new pharmaceutical products, since nearly half of the active substances being identified through the new paradigm in high through put screening are either insoluble or poorly soluble in water. The rate of dissolution of a drug is a function of its intrinsic solubility and its particle size. Studies with poorly soluble drugs have demonstrated that particle size reduction to the sub-micron range can lead to an increase in dissolution rate and higher bioavailability.

In aqueous systems, Fenofibrate has a poor solubility and displays no amphiphilic character. Therefore the drug is molecularly dispersed in water until the solubility product of Fenofibrate is exceeded. The poor dissolution rate of such water-insoluble drugs confronts a major obstacle in development of pharmaceutical dosage forms. The oral absorption of these drugs is often controlled by dissolution in GI tract. Thus dissolution of drug is of prime importance in

absorption. The different techniques used to enhance the dissolution of water insoluble drugs, some of them are particle size reduction, surfactant as solublizing agent, drug complex with hydrophilic carrier, pro-drug approach, formulation of drug as solid solution to improve the dissolution rate by decreasing the crystallinity. Among these the most promising method for promoting dissolution is the use of Liquisolid compacts.

Fenofibrate a very slightly water soluble drug was formulated into Liquisolid compacts consisting of similar powder excipients with different liquid vehicles. The in-vitro drug dissolution rates of such preparations were compared to those of conventionally prepared directly compressed tablets using a USP-II apparatus.[3]

1.1 PRINCIPLE OF LIQUISOLID COMPACTS[4]

With the liquisolid technology, a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected excipients named the carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is incorporated into the porous carrier material.

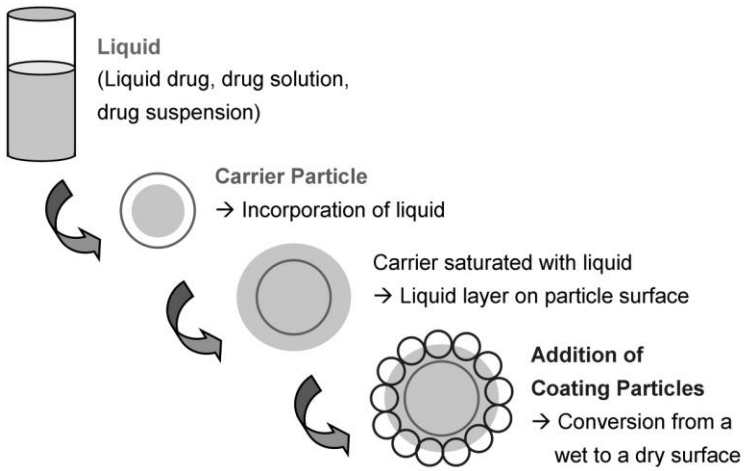


Fig no .1.1- Schematic representation of liquisolid systetem

The term 'liquisolid systems' is a powdered form of liquid drug formulated by converting liquid lipophilic drug or drug suspension or solution of water-insoluble solid drug in suitable non-

volatile solvent systems, into dry looking, nonadherent, free-flowing and readily compressible powdered mixtures by blending with selected carrier and coating materials. Various grades of cellulose, starch, lactose, etc. are used as the carriers, whereas very fine silica powder is used as the coating (or covering) material. .[4] The good flow and compression properties of Liquisolid may be attributed due to large surface area of silica and fine particle size of avicel. Hence Liquisolid compacts containing water-insoluble drugs expected to display enhanced dissolution characteristics and consequently improved oral bioavailability.[2,3]

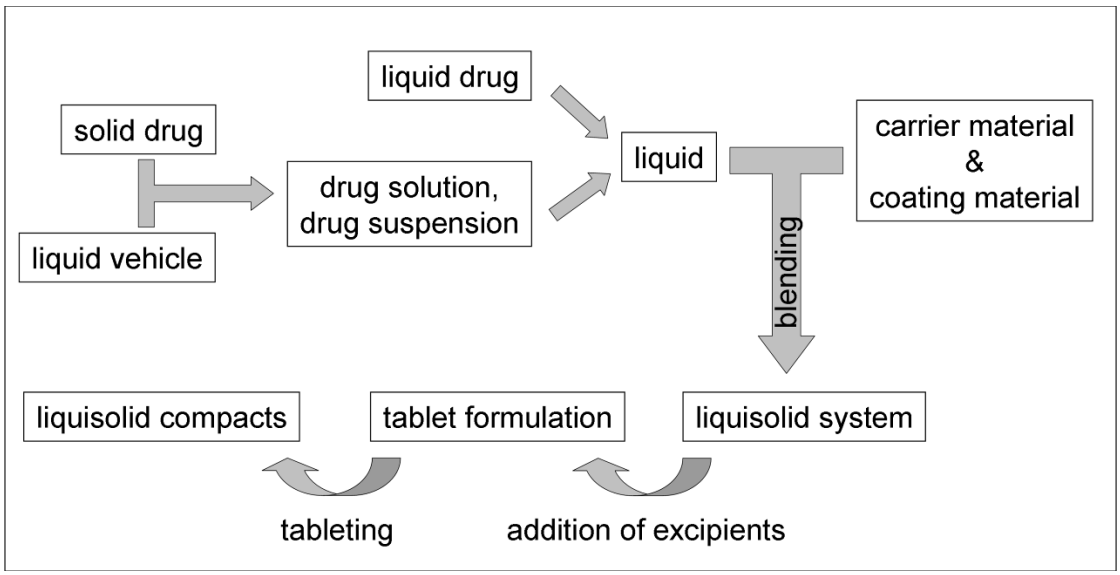


Fig no.1.2--Schematic outline of the steps involved in the preparation of liquisolid compacts

Liquisolid systems are acceptably flowing and compressible powdered forms of liquid medications. According to the concept of iquisolid systems, liquid lipophilic drugs, or water-insoluble solid drugs dissolved in suitable non-volatile solvents, may be converted into free-flowing and readily compressible powders by a simple admixture with selected powder excipients referred to as the carrier and coating materials. Various grades of Microcrystalline or amorphous cellulose may be used as carrier, whereas very fine particle size Silica powders may be used as coating materials. This review covers the detail aspects of Liquisolid formulation technique for solubility enhancement of poorly soluble drugs. Improved drug release profiles are exhibited by such formulations for poorly soluble drugs.[5]

1.2 Suitability of liquisolid technique[6]

1-Water insoluble drugs.

2-Lipophilic or highly permeable drugs.

3-Drugs having slow dissolution rate.

4-Low dose drugs [6]

5- Drugs having slow disintegration rate

6- Drugs having poor oral bioavailability.

1.3 Advantages of Liquisolid Compact[7,8]

1.A great number of slightly and very slightly water-soluble and practically water-insoluble liquid and solid drugs such as Digitoxin, Prednisolone,Fenofibrate, Atorvastatin and Hydrocortisone etc. can be formulated into liquisolid systems using the new formulation mathematical model.

2. Better availability of an orally administered water-insoluble drug is achieved when the drug is in solution form.

3. Though the drug is in a tabletted or encapsulated dosage form it is held in a solubilized liquid state, which consequently contributes to increased drug wetting properties, thereby enhancing drug dissolution.

.

4. Production cost of liquisolid systems is lower than that of soft gelatin capsules.

5.Liquisolid systems exhibit enhanced drug release.

6. Optimized rapid-release liquisolid tablets or capsules of water-insoluble drugs exhibit enhanced in-vitro and invivo drug release as compared to their commercial counterparts.

7. Optimized sustained-release liquisolid tablets or capsules of water-insoluble drugs exhibit surprisingly constant dissolution rates (zero-order-release) comparable only to expensive commercial preparations that combine osmotic pump technology and laser-drilled tablets 20.

8 . Low dose drugs can be formulated.

9. Can be used in controlled drug delivery.

10.Drug release can be modified using suitable formulation ingredients

11. Drug can be molecularly dispersed in the formulation.

12. Capability of industrial production is also possible.

1.4 Disadvantages of Liquisolid System[9,10]

1.The liquisolid systems have low drug loading capacities and they require high solubility of drug in non-volatile liquid vehicle.

2. It requires more efficient excipients which have higher adsorption capacities which provide faster drug release with smaller tablet size to improve liquisolid formulations.

3. To maintain acceptable flowability and compatibility for liquisolid powder formulation high levels of carrier and coating materials are require and that in turn will increases the weight of each tablet above 1 gm which is very difficult to swallow .

1.5 Mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts[11,12]

Several mechanisms of enhanced drug release have been postulated for liquisolid systems. The three main suggested mechanisms include an increased surface area of drug available for release, an increased aqueous solubility of the drug, and an improved wettability of the drug particles. Formation of a complex between the drug and excipients or any changes in crystallinity of the drug could be ruled out using DSC and XRPD measurements.

A. Increased drug surface area

If the drug within the liquisolid system is completely dissolved in the liquid vehicle it is located in the powder substrate still in a solubilized, molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablet.

B. Increased aqueous solubility of the drug

In addition to the first mechanism of drug release enhancement it is expected that *Cs*, the solubility of the drug, might be increased with liquisolid systems. In fact, the relatively small amount of liquid vehicle in a liquisolid compact is not sufficient to increase the overall solubility of the drug in the aqueous dissolution medium. However, at the solid/liquid interface between an individual liquisolid primary particle and the release medium it is possible that in this microenvironment the amount of liquid vehicle diffusing out of a single liquisolid particle together with the drug molecules might be sufficient to increase the aqueous solubility of the drug if the liquid vehicle acts as a co-solvent.

C. Improved wetting properties

Due to the fact that the liquid vehicle can either act as surface active agent or has a low surface tension, wetting of the liquisolid primary particles is improved. Wettability of these systems has been demonstrated by measurement of contact angles and water rising times.

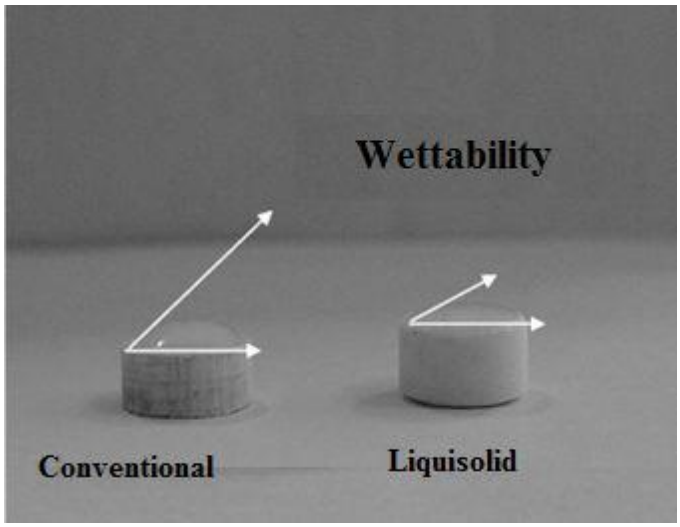


Fig no 1.3- Comparison of wettability between Conventional tablet and liquisolid compacts

1.6 Classification of liquisolid systems[13,14,15]

A. Based on the type of liquid medication contained therein, liquisolid systems may be classified into three subgroups :-

1. Powdered drug solutions
2. Powdered drug suspensions
3. Powdered liquid drugs

The first two may be produced from the conversion of drug solutions or (e.g. prednisolone solution in propylene glycol13 drug suspensions (e.g. gemfibrozil suspension in polysorbate 8032, and the latter from the formulation of liquid drugs (e.g. clofibrate, liquid vitamins, etc.) into liquisolid systems.

B. Based on the formulation technique used, liquisolid systems may be classified into two Categories :-

1. Liquisolid compacts
2. Liquisolid Microsystems

1.7 Components of Liquisolid Compact Formulation[16,17,18]

Liquisolid compact mainly includes

1. Non volatile solvent
2. Disintegrant
3. Drug candidate
4. Carrier material
5. Coating material

Non volatile Solvent:-

Non volatile Solvent should be Inert, high boiling point, preferably water-miscible and not highly viscous organic solvent systems and compatible with having ability to solubilise the drug. The non volatile solvent acts as a binding agent in the liquisolid formulation.

Disintegrant:-

Super disintigrants increases the rate of drug release, water solubility and wettability of liquisolid granules.

Drug candidates

This technique was successfully applied for low dose BCS class II and class IV drugs which are poorly water soluble and have slow dissolution rate.

Carrier Materials

Carrier material should be porous material possessing sufficient absorption properties which contributes in liquid absorption.The carrier and coating materials can retain only certain amounts of liquid and at the same time maintain acceptable flow and compression properties hence, increasing moisture content of carrier's results in decreased powder flowability .

Coating Materials

Coating material should be a material possessing fine and highly adsorptive particles which contributes in covering the wet carrier particles and displaying a dry-looking powder by

adsorbing any excess liquid.Coating material is required to cover the surface and so maintain the powder flowability.

Examples of these components:-

Solvents: Non-volatile solvents like PEG 600 and 400, Tween80 and 20, Span80 and 20, Glycerin, propylene glycol etc.

Carrier materials: Various grades of microcrystalline cellulose such as pH101and 200 Starch 1500, Fujicalin etc.

Hydrophobic carrier: Eudragit RL and RS , HPMC K4M,(sustained release) etc.

Coating material: Aerosil 200 , silica (Cab-O-Sil M5), Syloid etc.,

Disintegrants: Sodium starch glycolate, cross carmelose sodium, cross povidine, explota, Pregelatinized Starch .

Drug candidates: carbamazepine, famotidine, piroxicam, indomethacin, hydrocortisone, naproxen, fenofibrate, atorvastatin, prednisolone, digoxin, digitoxin, hydrocortisone, spironolactone, hydrochlorothiazide, polythiazide.

General method of preparation[20]

Firstly BCS class II drug (Fenofibrate) is dispersed in a nonvolatile vehicle (propylene glycol-PEG 200).Then a binary mixture of carrier coating materials (Microcrystalline cellulose as the carrier powder and silica as the coating material in a ratio of 20:1) was added to the mixture containing the drug and propylene glycol under continuous triturating in a mortar and pastel. Finally, disintegrant (sodium starch glycolate) was mixed and triturate with the resultants mixture for a period of 5 minutes.Then we add binder (talc) for the hardness of tablets. So that by using this methodology we get liquisolid compact of fenofibrate.Then we compress the tablets of Fenofibrate by using Tablet punching machine.

The liquid vehicle can either act as surface active agent or has a low surface tension, wetting of the liquisolid primary particles is improved. If the drug within the liquisolid system is completely dissolved in the liquid vehicle it is located in the powder substrate still in a solubilized, molecularly dispersed state. Therefore, the surface area of drug available for release is much greater than that of drug particles within directly compressed tablet.

The term 'liquisolid systems' is a powdered form of liquid drug formulated by converting liquid lipophilic drug or drug suspension or solution of water-insoluble solid drug in suitable non-volatile solvent systems, into dry looking, nonadherent, free-flowing and readily compressible powdered mixtures by blending with selected carrier and coating materials. Various grades of cellulose, starch, lactose, etc. are used as the carriers, whereas very fine silica powder is used as the coating (or covering) material. .[4] The good flow and compression properties of Liquisolid may be attributed due to large surface area of silica and fine particle size of avicel. Hence Liquisolid compacts containing water-insoluble drugs expected to display enhanced dissolution characteristics and consequently improved oral bioavailability

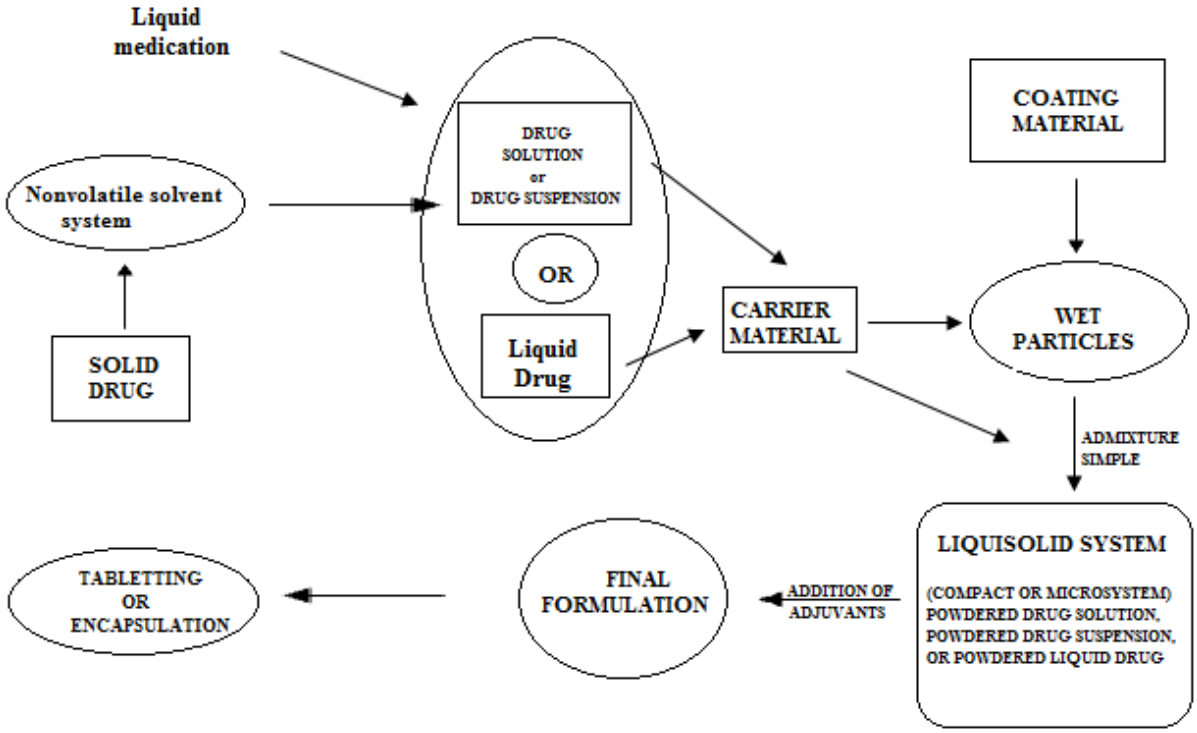


Fig no 1.4-General method for formulation of liquisolid compact

1.8 Application of the mathematical model for designing liquisolid compacts[21,22]

The flowability and compressibility of liquisolid compacts are addressed simultaneously in the 'new formulation mathematical model of liquisolid systems', which was used to calculate the appropriate quantities of the carrier and coating materials required to produce acceptably flowing and compressible powders based on new fundamental powder properties called the flowable liquid retention potential (Φ -value) and compressible liquid retention potential (Ψ -number) of the constituent powders. The Flowable Liquid Retention Potential of a powder is defined as the maximum amount of a given non-volatile liquid that can be retained inside its bulk (w/w) while maintaining acceptable flowability. The Compressible Liquid Retention Potential (Ψ) of a powder is the maximum amount of liquid, the powder can retain inside its bulk (w/w) while maintaining acceptable compactability, to produce compacts of suitable hardness and friability, with no liquid squeezing out phenomenon during the compression process. The Φ value of powders may be determined using a new procedure, the liquisolid flowability (LSF) test. The Ψ number of powders may be determined using a new method termed the liquisolid compressibility (LSC) test which employs the 'pactisity theories' to evaluate the compaction properties of liquid/ powder admixtures. According to the new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties. Depending on the excipients ratio (R) or the carrier: coating ratio of the powder system used, where,

$R = Q/q$ …..(1)

As R represents the ratio between the weights of carrier (Q) and coating (q) materials present in the formulation. An acceptably flowing and compressible liquisolid system can be prepared only if a maximum liquid on the carrier material is not exceeded; such a characteristic amount of liquid is termed the liquid load factor (Lf) and defined as the ratio of the weight of liquid medication (W) over the weight of the carrier powder (Q) in the system, which should be possessed by an acceptably flowing and compressible liquisolid system. i.e.:

$Lf = W/Q$ …..(2)

The powder excipients ratios R and liquid load factors Lf of the formulations are related as follows:

$\Phi Lf = \Phi + \Phi (1/R)$ …..(3)

In order to calculate the required ingredient quantities, the flowable liquid retention potentials (Φ-values) of powder excipients were utilized . So to calculate the required weights of the excipient used, first, from Eq. (3), Φ and Φ and are constants, therefore, according to the ratio of the carrier/ coat materials (R), Lf was calculated from the linear relationship of Lf versus 1/R. Next, according to the used liquid vehicle concentration, different weights of the liquid drug solution (W) will be used. So, by knowing both Lf and W, the appropriate quantities of carrier (Q) and coating (q) powder materials required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system could be calculated from equations (1) and (2).

Determination of flowable liquid retention potential (*Φ*- value).[23]

The liquisolid flowability (LSF) test is employed to determine the flowable liquid retention potential (Φ-value) of several powder excipients likely to be included in liquisolid compacts. The test is basically a titration-like procedure in which 25 to 30 grams of mixtures of the powders under investigation, with increasing amounts of a non-volatile solvent (i.e., liquid/solid weight composition), such as, for example, polyethylene glycol, light mineral oil and clofibrate, are prepared using a standard mixing process which ensures uniformity, and their flow rate and consistency are assessed using a recording powder flow meter (RPF). The liquid/solid weight composition (w/w) in that admixture, which just complies with a desired and preselected limit of acceptable flowability, is taken as the Φ- value of the excipient. The non-volatile solvent used in the LSF test should be the one selected to be included in the liquid medication (drug solution or drug suspension) of the targeted liquisolid product; where a liquid drug is formulated, then the LSF test should be conducted with the liquid drug itself. This value will change when different solvent or solvent system is employed.

Symbols and Definition:-

W = Liquid Weight of liquid medication

W = Solid Weight of carrier and coating material

Q = Weight of carrier powder material

Q = Weight of coating powder material

R = Powder excipient ratio

Lf = Liquid loading factor

Φ= Flowable liquid retention potential of the carrier powder

Φ = Flowable liquid retention potential of the coating powder

V = Total volume of liquid

VΦ =Total volume of liquid absorbed into carrier material

V φ =Total volume of liquid adsorbed into coating material

P = Density of liquid

1.9 Marketed preparations of liquisolid technique[24,25]

Brand name:- Mepron

Generic name:- Atovaquone

Brand name:- Infasurf

Generic name:- Calfactant

Brand name:- Dermotic oil

Generic name:- Fluocinolone Acetonide Oil Ear Drops

Brand name:- Proair HFA

Generic name:- Albuterol Sulfate Inhalation Aerosol

Brand name:- Maxalt

Generic name:- Rizatriptan Benzoate

Brand name:- Noritate

Generic name:- Metronidazole

Brand name:- Angeliq

Generic name:- Drospirenone and Estradiol

Brand name:- Renova

Generic name:- Tretinoin Cream

Brand name:- Sporanox oral solution

Generic name:- Itraconazole Oral Solution

1.10 Applications of liquisolid technique[26.27]

1. Enhanced solubility and dissolution rate

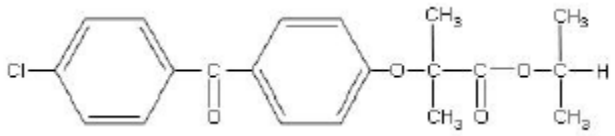
2. Enhancementsof bioavailability
3. Formulation of Sustained release tablets
4..Designing of controlled release tablets.
5. Application in probiotics.

1.11 DRUG PROFILE :-

Drug selected:- Fenofibrate[29,30]

Drug information:- Drug is official in British Pharmacopoeia

Chemical structure:-



Chemical name -propan-2-yl 2-{4-[(4-chlorophenyl)carbonyl]phenoxy}-2-methylpropanoate

Molecular formula:- $C_{20}H_{21}O_4Cl$

Molecular weight:- 360.83

Melting point:- 79°-82°C.

Log P:- 5.3

Solubility:- Insoluble in water, very soluble in methylene chloride, slightly soluble in ethanol.(96%)

Half-life- 20 hours

Adverse effects of Fenofibrate:- Fenofibrate has been associated with a rare but serious side effects:-

1. Abdominal Pain
2. Back Pain
3. Headache
4. Asthenia
5. Flu Syndrome
6. Diarrhea
7. Constipation
8. Liver Function Tests Abnormal
9. Respiratory Disorder

Mechanism of action:-

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of peroxisome proliferator-activated receptor type alpha (PPARα). Through activation of PPARα fenofibrate increases the lipolysis and elimination of atherogenic triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII. Activation of PPARα also induces an increase in the synthesis of apoproteins AI and AII, which leads to a reduction in very low- and low-density fractions (VLDL and LDL) containing apoprotein B and an increase in the high-density lipoprotein fraction (HDL) containing apoprotein AI and AII. In addition, through modulation of the synthesis and catabolism of VLDL fractions, fenofibrate increases the LDL clearance and reduces small and dense LDL, the levels of which are elevated in the atherogenic lipoprotein phenotype, a common disorder in patients at risk for coronary heart disease.

Pharmacokinetics:-

Bioavailability:-15 to 20%

Protein binding:-99%

Half life:-20 hrs

Clinical Pharmacology:-

Absorption: The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract.

Distribution: In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within a week of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum proteinbinding was approximately 99% in normal and hyperlipidemic subjects.

Metabolism: Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

Excretion: After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

1.12 EXCIPIENTS PROFILE:

1. MICROCRYSTALLINE CELLULOSE[31]

Non proprietary Names : Microcrystalline cellulose,Cellulosum microcrystallinum.

Empirical formula : $(C_6H_{10}O_5)$ n Where n = 220

Molecular weight : 36000

Applications

It is used primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. It has also got some lubricant, anti-adherent, and disintegrating properties, which make it useful in tabletting.

Typical Properties

Angle of repose **:** 34.4°

Density (bulk) **:** 0.337g/cm3

Density (tapped) **:** 0.478g/cm3

Flow ability **:** 1.41 g/s

Melting point **:** chars at 260 - 270°C.

Incompatibilities

Incompatible with strong oxidizing agents.

2. STARCH[32]

Nonproprietary Names:

BP: Maize starch

USPNF: Corn starch

JP: Corn starch

Synonyms:

Amido; amidon; amilo; amylum

Chemical Name:

Starch

Empirical Formula and Molecular Weight: (C6H10O5)n and 50 000–160 000

Starch occurs as an odorless and tasteless, fine, white-colored powder comprising very small spherical or ovoid granules whose size and shape are characteristic for each botanical variety.

Stability and Storage Conditions:

Dry, unheated starch is stable if protected from high humidity. When used as a diluent or disintegrant in solid-dosage forms, starch is considered to be inert under normal storage conditions. However, heated starch solutions or pastes are physically unstable and are readily attacked by microorganisms to form a wide variety of starch derivatives and modified starches that have unique physical properties.

Applications in Pharmaceutical Formulation or Technology:

Starch is used as an excipient primarily in oral solid-dosage formulations where it is utilized as a binder, diluent, and disintegrant. In tablet formulations, freshly prepared starch paste is used at a concentration of 5–25% w/w in tablet granulations as a binder. Starch is one of the most commonly used tablet disintegrants at concentrations of 3–15%W/w.

3. SODIUM STARCH GLYCOLATE[33]

Nonproprietary Names

NF: sodium starch glycolate

BP: sodium starch glycolate

Synonyms:

Sodium carboxy, methyl starch, explotab, primojel

Functional category:

USP: Tablet disintegrant

Others: Tablet and capsule disintegrant

Chemical names:

Starch carboxyl methyl ether, sodium salt

Description:

White to off- white, odourless, tateless, free flowing powder microscopic: oval or spherical granules, 30-100µm in diameter with some less spherical granules ranging from 10-35 µm in diameter.

Typical properties:

Density: 1.5 gm/cm3

Bulk volume: 1.4 gm/cm3; sodium chloride: 5% (Max); viscosity [2% solution, Brookfield : 25cps (max)]

Solubility: at 2% W/V, it disperses in cold water and settles in the form of a highly form a highly saturated layer. Insoluble in organic solvents.

Stability and storage conditions:

Stable, store in a well closed container to protect it from wide variations in humidity and temperature that may cause caking. It has long shelf life stability.

Incompatibilities:

No citation found.

Application in pharmaceutical formulations or technology:

It is used in tablet/capsule as disintegrant (wet granulation or direct compression) with concentration range 2-10 %.

4. AEROSIL[34]

Nonproprietary Names:

BP: Colloidal anhydrous silica

USPNF: Colloidal silicon dioxide

Synonyms:

Colloidal silica; fumed silica; light anhydrous silicic acid; silicic anhydride; silicon dioxide fumed.

Chemical Name:

Silica

Empirical Formula and Molecular Weight:

SiO2 and 60.08

Functional Category:

Adsorbent; anticaking agent; emulsion stabilizer; glidant; suspending agent; tablet disintegrant; thermal stabilizer; viscosity-increasing agent.

Description:

Aerosil is submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, nongritty amorphous powder.

Stability and Storage Conditions:

Aerosil is hygroscopic but adsorbs large quantities of water without Liquefying. Colloidal silicon dioxide powder should be stored in a well-closed container.

Applications in Pharmaceutical Formulation or Technology:

Aerosil is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations. Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders.

1.13 REVIEW OF LITERATURE[35-70]

1-**Sanjeev Gubbi et al[5] (1986)** studied that liquisolid technique is a promising alternative for improvement of dissolution property of water-insoluble drugs, such as BXH. The higher dissolution rate showed by Liquisolid compacts may imply enhanced oral bioavailability due to the increased wetting properties and surface of drug available for dissolution. The Liquisolid compact of BXH made in propylene glycolshowed better dissolution rate than BXH with PEG 400based upon solubility and molecular fraction (FM) of thedrug in their liquid medication.

2-**V.B.Yadav et al[6] (1986)** studied that liquisolid system refers to formulations formedby conversion of liquid drugs, drug suspensions or drug solution in non-volatile solvents into dry, nonadherent, free-flowing and compressible powder mixtures by blending the suspension or solution with selected carriers. The formed liquisolid tablets dosage form showed significantly greater extent of absorption due to their solubility and dissolution improvement. The technique is also used to design sustained release systems by using hydrophobic carriers instead of hydrophilic carries in liquisolid systems. Therefore, this formulation of the drug has the potential to be considered for human study in order to be manufactured on a large scale.

3-**Javadzadeh Y et al[7] (1986)** studied that liquisolid technique has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. In the present study, propranolol hydrochloride was dispersed in polysorbate 80 as the liquid vehicle. Then a binary mixture of carrier-coating materials (Eudragit RL or RS as the carrier and silica as the coating material) was added to the liquid medication under continuous mixing in a mortar. The final mixture was compressed using the manual tableting machine. The effect of

drug concentration, loading factor, thermal treating and aging on release profile of propranolol hydrochloride from liquisolid compacts were investigated at two pH values (1.2 and 6.8).

4-**Babatunde Akinlade et al[8] (1987)** studied that based on the nature of the drug and the non-volatile liquid vehicle used, liquisolid technique has the capability to increase furosemide intrinsic solubility. Liquisolid tablets containing Synperonic® PE/L as a new liquid vehicle exhibited greater dissolution due to the physical properties of this liquid vehicle which led to increased wetting properties and solubility of the drug; demonstrating higher drug release than those of conventionally made tablets (which failed as well friability test and could not withstand). PEG 400 as a liquid vehicle failed to improve furosemide dissolution owing to lower solubility of the drug in PEG 400 compared to Synperonic® PE/L and possible drug-PEG 400 interaction as revealed by DSC and FT-IR data. Since drug dissolution is the rate limiting step in oral drug absorption of non-polar molecules, liquisolid compacts prepared with Synperonic® PE/L 81 might present substantial in vivo superiority over conventional directly compacted counterpart. Caprol®. PGE 860 was not a good choice of liquid vehicles to prepare furosemide liquisolid tablets. There is no single liquid vehicle which is suitable for all poorly water soluble drugs to formulate liquisoid compacts. Accordingly, choosing a suitable liquid vehicle, depending on its properties e.g. viscosity, for a particular drug is important to prepare a successful liquisolid tablets.

5-**Santosh Kumar.K et al[9] (1987)** studied that Liquisolid technique gives a design to enhance the absorption as well as dissolution rate their by it may enhance the bio availability of a poorly soluble, insoluble or lipophilic drug and to formulate them into immediate release or else sustain release by selection of suitable solvent and carrier.

6-**Amrit B Karmarka et al [10] (1990)** studied that Liquisolid formulations are designed to contain liquid medications in powdered form,and hence possess drug delivery mechanisms similar to that of soft gelatin capsule preparations containing liquids. This novel technique is found to be efficient method for formulation of water insoluble solid drugs and liquid lipophilic drugs.

7-**Yousef Javadzazeh et al[11] (1990)** studied that Liquisolid formulations were designed to contain liquid medications in powdered form, thereby possessing mechanisms of drug delivery similar to those of soft gelatin capsule preparations containing liquids. The results showed that

the liquisolid technique could be a promising alternative technique to increase the dissolution of water insoluble drugs. The results of DSC and X-ray crystallography ruled out any changes in crystallinity of the drug or any interaction between the drug and exipients during the formulation process. It was shown that aging had no significant effects on dissolution profile of indomethacin liquisolid tablets.

8-**Hitendra S. Mahajan et al[12] (1991)** studied that The wettability of the compacts by the dissolution media is one of the proposed mechanisms to explain the enhanced dissolution rate of glipizide from liquisolid tablets. The aim of improving dissolution rate and bioavailability of poorly soluble glipizide was successful because of increased wetting properties and solubility of drug in liquid vehicles. Use of mathematical model for calculating amounts of excipients helps in optimizing these formulations. Though all the three liquid vehicles used increase solubility of glipizide, PEG 400 was found as the best among them. Treated gellan gum was found to be an excellent disintegrating agent as compared to sodium starch glycolate.

9-**K. Rajesh et al (1991)** studied that Liquisolid system contains liquid medications in powdered form and this novel technique is an efficientmethod for formulating water insoluble drugs. Rapid disintegration rates are observed compared to conventional tablets showed improved release rates and greater bioavailability. The use of non-volatile solvent causes increased wettability and ensures molecular dispersion of drug in the formulation. By using hydrophobic carriers can modify release (sustained release) of drugs from the liquisolid tablets.

10-**Venkat B.Yadav et al[14] (1991)** studied that liquisolid and compaction granulation technique has been proved to be a imperative development to increase the solubility, dissolution rate and other physicochemical characteristics of LT, GF and FF using PEG-400 a hydrophilic binder,silca as absorbent/coating material, microcrystalline cellulose and sodium starch glycolate as excipients in granulation technique. Adsorption of hydrophilic excipients on drug substances significantly increases the drug solubility, wettability and dissolution rate and flowability. In addition, the adsorption of any organic residual solvent in the final formulation avoided because of elimination of use of organic solvents for preparation of granules. Crystallinity of the prepared granules is reduced due to drug–excipients interaction in formulation obtained using compaction and liquisolid granulation technique without any chemical interaction premeditated by FTIR.

11- **Amrit B Karmarkar et al (1991)** studied that liquisolid system is a novel concept of drug delivery via oral route. This technique is applied to water insolubl dissolving the drug in suitable non-volatile solvent and then adding this liquid medication to the mixture of carrier and coating materials. Mixing of this will lead to liquisolid system which is subjected to tabletting by direct compression. Increase in dissolution rate and in turn improvement in bioavailability is observed in case of poorly water soluble drugs. However, sustained effect is achieved in case of water soluble drugs. By use of this technique, liquid medications such as solutions or suspensions of water insoluble drugs in suitable non-volatile liquid vehicles can be easily converted into powder with acceptable flow properties and compression behavior using suitable powder excipients.

12- **Avinash H Hosmani et al (1991)** studied that liquisolid technique has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. In the present study, propranolol hydrochloride was dispersed in polysorbate 80 as the liquid vehicle. Then a binary mixture of carrier-coating materials (Eudragit RL or RS as the carrier and silica as the coating material) was added to the liquid medication under continuous mixing in a mortar. The final mixture was compressed using the manual tableting machine. The effect of drug concentration, loading factor, thermal treating and aging on release profile of propranolol hydrochloride from liquisolid compacts were investigated at two pH values (1.2 and 6.8). The release rate of propranolol HCl from liquisolid compacts was compared to the release of propranolol HCl from conventional tablets.

13- **Pandurang N Dhabale et al (1994)** studied that the dissolution properties of a drug and its release from a dosage form have a basic impact on its bioavailability. Solving solubility problems is a major challenge for the pharmaceutical industry with developments of new pharmaceutical products. There are various methods but liquisolid technique is a new and promising method that can change the dissolution rate of water insoluble drugs. According to the new formulation method of liquisolid compacts, liquid medications such as solutions or suspensions of water insoluble drugs in suitable nonvolatile liquid vehicles can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. It has been speculated that such systems exhibit enhanced release profiles.

14- **Satish B Bhise et al (1994)** studied that liquisoild technique is a novel concept for delivery of drugs through oral route. This approach of delivering drugs is suitable mostly for lipophilic drugs and poorly or water insoluble drugs. This approach is suitable for immediate or sustain release formulations. Design and formulation of this approach is prescribed according to new mathematical model given by Spires et al. Increasing the solubility by using a non-volatile solvent which is suitable for drug, their by dissolving the drug in the non volatile solvent and this is termed as liquid medicament . Blending the liquid medicament with mixture of carrier and coating material, liquid medicament can be converted into non adhere, dry looking powder with acceptable flow properties and compression behavior using suitable excipients and tabletting by direct compression method.

15- **J. Umamaheswari et al[12] (1994)** studied that liquisolid technique is a new approach for delivery of drugs through oral route. This technique is suitable for poorly or water insoluble drugs and also for immediate or sustained release formulations. Design of this technique was according to new mathematical model proposed by Spireas *et al*. The drug is dissolved or dispersed in suitable non-volatile solvent and this liquid medication is converted to free flow powder by using carrier and coating material. To this suitable excipients were added and tabletting by direct compression.

16- **Vijay kumar Nagabandi et al**, **(1994)** studied that at present 40% of the drugs in the development pipelines, and approximately 60 % of the drugs coming directly from synthesis are poorly soluble. The limited solubility of drugs is a challenging issue for industry, during the development of the ideal solid dosage form unit. Liquisolid technique is a novel and promising approach to overcome this consequence. The technique is based upon the dissolving the insoluble drug in the nonvolatile solvent and admixture of drug loaded solutions with appropriate carrier and coating materials to convert into acceptably flowing and compressible powders. The selection of non toxic hydrophilic solvent, carrier, coating materials and its ratios are independent of the individual chemical moieties. The increased bioavailability is due to either increased surface area of drug available for release, an increased aqueous solubility of the drug, or improved wettability of the drug particles.

17- **T.Ramarao et al[4] (1996)** studied that to improve water solubility and drug release, respectively, among which the liquisolid technology is one of the most promising approaches.

With this technology liquids such as solutions or suspensions of poorly soluble drugs in a non-volatile liquid vehicle are converted into acceptably flowing and compressible powders by simple physical blending with selected excipients named the carrier and the coating material. As highest drug release rates are observed with liquisolid compacts containing a drug solution as liquid portion, liquisolid compacts may be optimized by selection of the liquid vehicle and the carrier and coating materials. Moreover, the addition of disintegrants may further accelerate drug release from liquisolid compacts.

18- **Sambasiva Rao et al[17] (1996)** studied that The bioavailabilty of many poorly water-soluble drugs is limited by their dissolution rates which are inturn controlled by the effective surface area present for dissolution. The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. The poor dissolution characteristics of water-insoluble drugs have long been a problem to the pharmaceutical industry. A more recent technique, **"**powdered solution technology" or "Liquisolid technology", has been applied to prepare water-insoluble drugs into rapid-release solid dosage forms. Inspite of formulating the drug in a tableted or an encapsulated dosage form, it is held in solution thus enhancing its release.

19- **Naga Aparna et al[9] (1996)** studied that Liquisolid systems refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water insoluble solid drugs in suitable nonvolatile solvent systems, into dry, non-adherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.

20- **Leila Musaalrezaei et al,[2] (1999)** studied that A "liquisolid system" refers to formulations formed by conversion of liquid drugs, drug suspensions or drug solution in nonvolatile solvents into dry, non-adherent, free-flowing and compactible powder mixtures by blending the suspension or solution with selected carriers and coating materials. Simplicity, low cost and capability of industrial production are some of the advantages of this technique.

21- **Ali Nokhodchi et al,[11] (2007)** studied that liquisolid technique can be optimized for the production of sustained release matrices of water-soluble drugs. Polysorbate 80 was used as the

liquid veh release kinetics. This investigation provided evidence that polysorbate 80 (Tween 80) has important role in sustaining the release of drug from liquisolid matrices. Heat treatment had no effect on release profile of drug from liquisolid tablets. Hardness and dissolution profile of drug were not affected by aging. No crystallinity change was observed during the process of liquisolid formulation. The proposed new technique can be used in the preparation of sustained release formulations of water-soluble drugs such as propranolol hydrochloride.

22- Mohammad reza siahi et al[10] (2007) studied that Liquisolid formulations were designed to contain liquid medications in powdered form, thereby possessing mechanisms of drug delivery similar to those of soft gelatin capsule preparations containing liquids. The results showed that the liquisolid technique could be a promising alternative technique to increase the dissolution of water insoluble drugs. The results of DSC and X-ray crystallography ruled out any changes in crystallinity of the drug or any interaction between the drug and exipients during the formulation process. It was shown that aging had no significant effects on dissolution profile of indomethacin liquisolid tablets.

23- **Avinash hosmani et al[5] (2007)** studied that the developed melt solidification technique is simple, single step. The beads obtained were non disintegrating, excipient free and show acceptable flow properties. The beads obtained by MSB2 method take 1-2 min crystallization time which might be due to low melting point and its poor aqueous solubility of fenofibrate (which results in insolubility of melt in water). Thus the present technique of melt solidification of fenofibrate serves to effective as it takes low processing time, convenient methodology, as compared to conventional particle size enlargement techniques.There is need of improvement of this technique further for extending release with use of proper
additives and process variables.

24- **Pandurang n. dhabale et al[12] (2007)** studied that Fenofibrate like drugs show amorphous nature and hence have poor flow properties. It also has low melting point of about 79-820 C. Hideji et al. [8] reported a method for particle size enlargement of ibuprofen. The same method was used here for fenofibrate which involves melting Fenofibrate powder and cooling the melt. The solidified mass of Fenofibrate was then crushed into granules. The multi-step process of particle size enlargement has been made to single step process to get Fenofibrate beads of desired flow properties.

25- **Satish b. bhise et al[14] (2007)** studied that developed melt solidification technique is simple, single step. The beads obtained were non disintegrating, excipient free and show acceptable flow properties. The beads obtained by MSB2 method take 1-2 min crystallization time which might be due to low melting point and its poor aqueous solubility of fenofibrate (which results in insolubility of melt in water). Thus the present technique of melt solidification of fenofibrate serves to effective as it takes low processing time, convenient methodology, as compared to conventional particle size enlargement techniques.There is need of improvement of this technique further for extending release with use of proper additives and process variables.

26- **Suria prabha.k et al[6] (2008)** studied that Liquisoild technique is a novel concept for delivery of drugs through oral route. This approach of delivering drugs is suitable mostly for lipophilic drugs and poorly or water insoluble drugs. This approach is suitable for immediate or sustain release formulations. Design and formulation of this approach is prescribed according to new mathematical model given by Spires et al. Increasing the solubility by using a non-volatile solvent which is suitable for drug, their by dissolving the drug in the non volatile solvent and this is termed as liquid medicament . Blending the liquid medicament with mixture of carrier and coating material, liquid medicament can be converted into non adhere, dry looking powder with acceptable flow properties and compression behavior using suitable excipients and tabletting by direct compression method.

27- **Satyanarayana.k et al[3], (2007)** studied that Because of drug present in the liquid medicament as solubilised or moleulary dispersed state, as the dissolution is enhanced due to increased surface area as well as wetting area. Their by the Liquisolid technique is applied for water insoluble drugs to enhance dissolution rate may also increase bioavailability.

28- **Raja hemanth kumar et al[23] (2007)** studied that Liquisolid compacts are derived from powdered solutions, An past technique based on conversion of a liquid medicament to nonadhere dry appearance powder which adsorb the medicament onto silicas of large specific Surfaces.These preparations were analyzed by dissolution studies but because they are present in the form of powder-dispersion they could not be compressed into tablets There after studies based on powder solutions, with direct compression enhancers like microcrystalline cellulose were added in solid dispersion to improve compressibility of systems.

29- **Ravindra jarag et al[11] (2008)** studied that The term ‘liquisolid systems’ (LS) is a powdered form of liquid drug formulated by converting liquid lipophilic drug or drug suspension or solution of water-insoluble solid drug in suitable non-volatile solvent systems, into dry looking, nonadherent, free-flowing and readily compressible powdered mixtures by blending with selected carrier and coating materials. Various grades of cellulose, starch, lactose, etc. are used as the carriers, whereas very fine silica powder is used as the coating (or covering) material. The good flow and compression properties of LS may be attributed due to large surface area of silica and fine particle size of avicel. Hence LS compacts containing water-insoluble drugs expected to display enhanced dissolution characteristics and consequently improved oral bioavailability

30- **J. Umamaheswari et al[6] (2008)** studied that In liquisolid technique the drugs which are insoluble or poorly soluble drugs are dissolved or dispersed in suitable non-volatile solvent and converted into free flow powder by using carrier material . The drug is present in the liquid medicament as solubilized or molecularly dispersed state, so the dissolution is enhanced due to increased surface area, wetting area and also increases bioavailability.

31- **Yadav VB et al[6], (2008)** studied that Liquisolid technique to improve the solubility and dissolution characteristics of a poorly water-soluble drug Fenofibrate (FNO). Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable polymers and surfactants. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because of bypassing drying step, the process is less time consuming and uses less energy than wet granulation. Granules were prepared by using hydrophilic polymer PEG (polyethylene glycol-6000) and surfactant (poloxomers-407). The prepared granules were characterized using powder XRD, DSC and FTIR techniques.

32- **Anjan K. Mahapatra et al[6] (2008)** studied that Among the various approaches to improve solubility, the solid Liquisolid technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble active pharmaceutical ingredients .

PROJECT OBJECTIVE:

I am preparing the liquisolid tablets of Fenofibrate because Fenofibrate has a poor solubility and displays no amphiphilic character. Therefore the drug is molecularly dispersed in water until the solubility product of Fenofibrate is exceeded.

There are various methods to enhance drug solubility but liquisolid technique is one of the promising technique The dissolution properties of a drug and its release from a dosage form have a basic impact on its bioavailability. Solving solubility problems is a major challenge for the pharmaceutical industry with developments of new pharmaceutical products, since nearly half of the active substances being identified through the new paradigm in high throughput screening are either insoluble or poorly soluble in water. The rate of dissolution of a drug is a function of its intrinsic solubility and its particle size. Studies with poorly soluble drugs have demonstrated that particle size reduction to the sub-micron range can lead to an increase in dissolution rate and higher bioavailability.

MATERIAL AND METHOD

Table no. 1.1 Materials used

S.No.	Materials	Grade	Name Of Supplier
1.	Finofibrate		Zydus cadila Gujrat
2.	Aerosil	L.R.	Loba Chemical, India.
3.	Sodium starch glycolate	L.R.	S.D. Fine Chem. Ltd. Mumbai.
4.	Starch	. L.R.	S.D. Fine Chem. Ltd. Mumbai.
5.	Microcrystalline Cellulose	LR	S.D. Fine Chem. Ltd. Mumbai.
6.	Talc	L.R.	S.D. Fine Chem. Ltd. Mumbai.
7.	Mg stearate	L.R.	S.D. Fine Chem. Ltd. Mumbai.

Equipments

Table no. 1.2 Equipments used and source

S. No.	Instruments	Source
1.	Electronic balance	Shimadzu Corporation--BL-220H, Japan
	Digital weighing balance	Sartorius Biotech (India) Pvt. Ltd.Bangalore
2.	UV/Visible spectrophotometer	Shimadzu 1700, Shimadzu Corporation. Japan
3.	FTIR spectrophotometer	Shimadzu, Shimadzu Corporation. Japan
4.	Stability chamber	EIE Instruments Pvt. Ltd.
5.	Electrolab disintegration apparatus	Electro lab.
6.	Electrolab dissolution apparatus (USPXXIII)	Electro lab.
7.	Oven	Shital Scientific Industries, Mumbai
8.	pH meter	Elico II-122
9.	Distillation unit	Biotech India, Mumbai
10	Tablet punching machine	Cadmach Machinery Co Ltd., Ahmedabad
11	Pan coating machine	Avon Engineering Works, Mumbai.
12	Friability test apparatus	Electrolab, Mumbai.

CHAPTER-2
PREFORMULATION

Preformulation studies are very important to develop the final dosage forms to the highest quality in the shortest time. It is essential that certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined, understood, and effectively utilized. This information dictates many of the subsequent events and approaches in formulation development. This first learning phase is known as preformulation.

- To minimize the errors.
- Formulation can be prepared easily.
- Learning before doing is also important.
- Reducing cost, increasing efficacy, bioavailability, solubility, dissolution rate for improved drug delivery.

Preformulation studies include :-

1-Preparation of calibration curve

2- Thin Layer Chromatography

3- Melting Point

4- Loss On Drying

5- Solubility Study

6-Partition Coefficient

7- Micrometrics Study

8- Drug Excipient Interaction(IR Analysis, TLC Analysis)

2.1 PREPARATION OF CALIBRATION CURVE

The drug is analysed by ultra-violet spectrophotometry. . It involves the measurement of the amount of the ultra violet (190-380nm) or visible (380-800 nm) radiation absorbed by a substance in solution .

A solution of Fenofibrate in methanol gives maximum absorbance at λ_{max} of 286.6 nm.

100µg/ml (1mg/ml) stock solution of drug was prepared in methanol and suitable dilutions were made i.e.5 µg/ml, 10 µg/ml, 15 µg/ml, 20 µg/ml, 25 µg/ml respectively. The sample was scanned using UV spectrophotometer, and λmax 286.6 nm was obtained. The absorbance of samples of different concentration at λmax (at 286.6 nm) were measured. The graph was plotted between the absorbance and concentration. The graph obeyed the Beer-Lambert's law in the selected concentration range. A linear relationship was observed over the range of 5-25µg/ml.

Table no.2.1 - Calibration curve of Fenofibrate:-

S.NO	CONCENTRATION(µg/ml)	ABSORBANCE
1	0	0
2	2	0.03
3	4	0.055
4	6	0.078
5	8	0.098
6	10	0.12

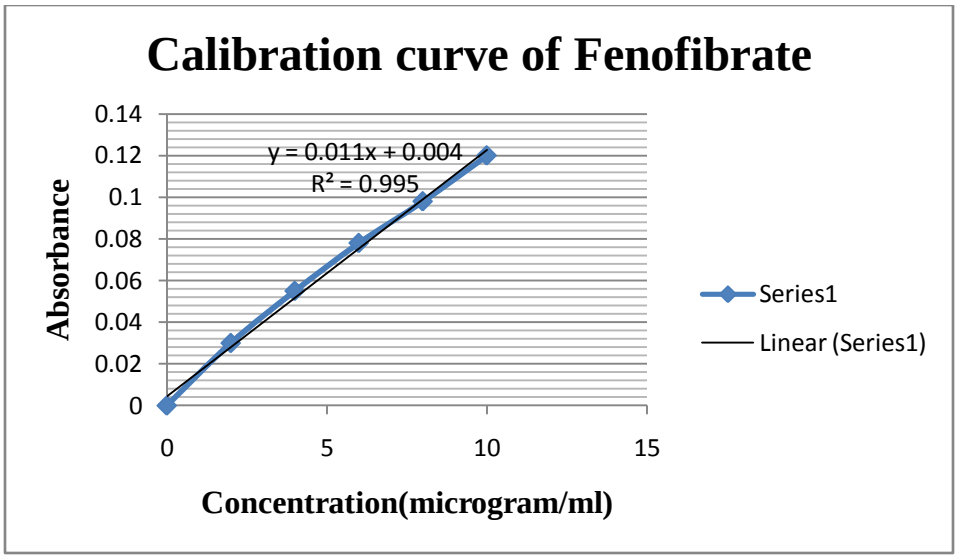


Fig no 2.1.- Caliberation curve of Fenofibrate

2.2- Thin Layer Chromatography [72]

Thin layer chromatography is an important analytical tool in the separation, identification and estimation of different drugs. In this technique the different compounds are separated by the difference in migration of solute between two phases, a stationary phase and a mobile phase. The principle of separation is adsorption and the stationary phases act as an adsorbent.

Preparation of TLC plates:-

Firstly we take the glass slide.Slurry is prepared separately by mixing silica gel G with water.Then we pour that slurry on glass slide uniformly.

Application of sample:-

The solution of Fenofibrate was made in methanol. About sample was spotted by capillary tube on TLC plates by keeping a distance of about 2 cm above the base of the plate. Allow it to dry in air.

Chromatogram :-

The plate was then placed in TLC chamber previously saturated with appropriate solvent system (Methanol,water 1:1 v/v) for the development of chromatogram, the plate was removed and the spot was observed under the UV chamber at the short wavelength 254nm, the principal spot in the chromatogram obtained. The Rf value was calculated and tabulated.

- **Stationary phase** = pre coated silica gel- G plate
- **Mobile phase** = Methanol: water, 1:1v/v

Rf value of Fenofibrate :-

Rf Value of Fenofibrate can be calculated by the following formula:

$$R_f = \frac{\text{Distance from start to center of substance spot}}{\text{Distance from start to solvent front}}$$

Table no 2.2-Rf value of Fenofibrate:-

Drug	**Rf Value**	**Reported Rf value**
Fenofibrate	0.40	0.42

2.3-Melting point of Fenofibrate

The measurement of melting point is a measure concern in pharmaceutical studies. The most important reason to determine melting point during preformulation is crystalline solubility such studies are particularly important because the scarcity of available drug powder often precludes accurate solubility determinations. Melting point and solubility are related via the latent heat of fusion, which is the amount of heat generated during melting or fusion.

Melting point was determined by digital auto melting point apparatus (decibel). Similar procedure was repeated here in this case. Automatically the temperature at which drug starts to melt was shown by digital auto melting point apparatus, noted and compared with literature value.[73]

It was found that melting point of drug is 80 ^{o}C.

2.4- Loss on drying :-

It can be calculated by the following formula :-

%LOD = WT OF WATER IN SAMPLE /TOTAL WT OF WET SAMPLE X 100

LOD is loss in wt in percentage weight/ weight resulting from water and volatile matter of any kind that can be driven off under specified condition(if substances is in form large crystal size reduced by rapid crushing to powder).

One gram of drug was kept in petridish, it was then covered and sample was distributed as evenly as possible by gentle shaking. Pertidish was placed in tray dryer at105^{-0}C. The sample was dried to constant weight After 4 hr it was found that loss on dry was 0.66%, which was, comply with specification as per limit (NMT 0.5%)[74]

Loss on drying was determined by keeping drug powder of known weight at 60◦ C and 0.7 K Pasc. for 4 hrs. and was found to be **0.66%**

2.5-Solubility studies :-

Solubility is defined in quantitative terms as the concentration of solute in a saturated solution at a certain temperature and in qualitative way; it may be defined as the spontaneous interaction of two or more substances to form a homogenous molecular dispersion.

The solubility of drug is an important physicochemical property because it affects the bioavailability of the drug, the rate of drug release into the dissolution medium, and consequently, the therapeutic efficacy of the pharmaceutical product. Preformulation solubility studies focus on drug-solvent system that could occur during the delivery of a drug candidate.[75]

Common solvents used for solubility are:

- Distill water
- PEG 200
- PEG 400
- Glycerine

Preparation of saturated solution:

The solubility of a material is usually determined by the equilibrium solubility method, which employs a saturated solution of the material, obtained by stirring an excess of material in the solvent for a prolonged period (24 hr) until equilibrium is achieved.

Analysis of saturated solutions:

The solution were filtered through sintered filter and absorbance were measured at 286.6 nm using UV spectrophotometer .

Table no 2.3-Solubility of drug in different solvents:

S No.	Solvent	Solubility(%W/W)	Volume of solvent in ml/gm of solute	Solubility
1	Distill water	0.0195	More than 10,000 part	Insoluble
2	PEG 200	7.93	1-10	Freely soluble
3	PEG 400	7.97	1-10	Freely soluble
4	Glycerine	3.91	More than 10,000	Slightly soluble

2.6- Partition coefficient :-

It is defined as the ratio of un-ionized drug distributed between the organic and aqueous phases at equilibrium

$$P_{o/w} = (C_{oil}/C_{water})_{equilibrium}$$

Partition coefficient (oil/water) is a measure of a drug's lipophilicity and an indication of its ability to cross cell membranes.

Drugs having values of log P much greater than 1 are classified as lipophilic, whereas those with partition coefficients much less than 1 are indicative of a hydrophilic drug[76]

Partition coefficient = concentration of drug in organic phase / concentration of drug in aqueous phase

Table no 2.4- Partition coefficient of Fenofibrate:-

Drug	**Log P**	**Reported Log P Value**
Fenofibrate	5.2	5.3

Log P = 5.3

2.7- Micrometrics Study[78-80]

A:Bulk density:

1 GM of pure drug was taken and fill in 10 ml capacity measuring cylinder and note the volume/height of drug filled.

Bulk density = mass of powder \ bulk volume of powder

B:Tapped density

1 GM of pure drug was taken and fills in 10 ml capacity measuring cylinder and tapped the measuring cylinder (100 times) until the constant height obtained note the volume/height of drug filled.

Tapped density = mass of powder \ volume of powder after tapping

C:Carr index:

Carr index = (Tapped density – Untapped density) / Tapped density

D: Angle of repose:

Angle of repose was determined in preformulation to find out the flow properties of drug. Placed a glass funnel on a ring supported by a stand, 4 gm of drug was taken and passed through funnel; maintain the gap between the bottom of the funnel and the top of powder from pile. After emptying the powder from the funnel measure the height of the pile and diameter[53, 56].

Angle of repose = tan Ø 2h/D

Where d=diameter, h= height

E. Hausner's ratio:-

Hausner's ratio can be calculated by this equation:-

Hausner's ratio $=D_{B\ max} / D_{B\ min}$

Table no 2.5 -Flowability parameters of fenofibrate liquisolid powder system:-

S.NO	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose	% Carr's index	Hausner's ratio	Flow of powder
LS-1.	0.34	0.566	39.65	30.12	1.45	POOR
LS-2.	0.314	0.480	38.26	19.21	1.36	GOOD
LS-3.	0.156	0.497	39.21	33.12	1.68	POOR
LS-4.	0.308	0.462	32.65	34.22	1.64	POOR
LS-5.	0.310	0.580	38.67	23.10	1.25	GOOD
LS-6.	0.298	0.447	35.74	20.02	1.29	GOOD
LS-7.	0.285	0.427	31.43	31.5	1.88	POOR
LS-8.	0.281	0.412	27.88	26.14	1.26	GOOD
LS-9.	0.318	0.413	41.97	22.12	1,83	GOOD
LS-10.	0.216	0.443	35.06	36.22	1.17	POOR
LS-11.	0.257	0.345	35.87	26.56	1.45	GOOD
LS-12.	0.212	0.546	36.76	39.53	1.41	GOOD
LS-13.	0.228	0.576	35.86	32.25	1.51	GOOD
LS-14.	0.328	0.446	33.86	39.24	1.75	POOR
LS-15.	0.318	0.445	36.96	40.22	1.65	POOR
LS-16.	0.316	0.468	38.76	33.21	1.33	POOR

Result:- Among all the batches, 2nd,5th,6th,8th,9th,11th batches are showing good flowability.

2.8-Drug excipient interaction [81]

The interaction studies can be done on the basis of U.V, Infra red and TLC analysis.

Thin layer chromatography is an important analytical tool in the separation, identification and estimation of different drugs. In this technique the different compounds are separated by the difference in migration of solute between two phases, a stationary phase and a mobile phase. The principle of separation is adsorption and the stationary phases act as an adsorbent

TLC analysis of drug interaction with excpients:-

- **Stationary phase** = pre coated silica gel- G plate
- **Mobile phase** = Methanol: water, 1:1v/v
- **Indicator =** Uv spectrophotomerty
- **Sample preparation:** Apply 20 µl of mixture of methanol containing 0.1%w/v of drug

The plate was spotted with standard solution at about 2 cm from the bottom. The sample solution was spotted adjacent to the pure drug spot at a distance of 2 cm. The plate was kept in a chamber saturated previously with the solvent system. The solvent was allowed to rise on the plate to a sufficient level. The distance traveled by the solvent front was noted. The distance traveled by the solute was determined by measuring the sample spot. The R_f value was calculated.

It was observed that the R_f values for the pure drug (Fenofibrate) and the mixture were proximal.

Table no 2.6- Thin layer chromatography of drug excipient interaction:-

S.NO	**Drug+ excipient**	**Rf value**
1.	Drug+PEG400	0.41
2.	Drug+ MCC	0.42
3.	Drug+silica	0.40

- **R_f Value of Fenofibrate = 0.40**

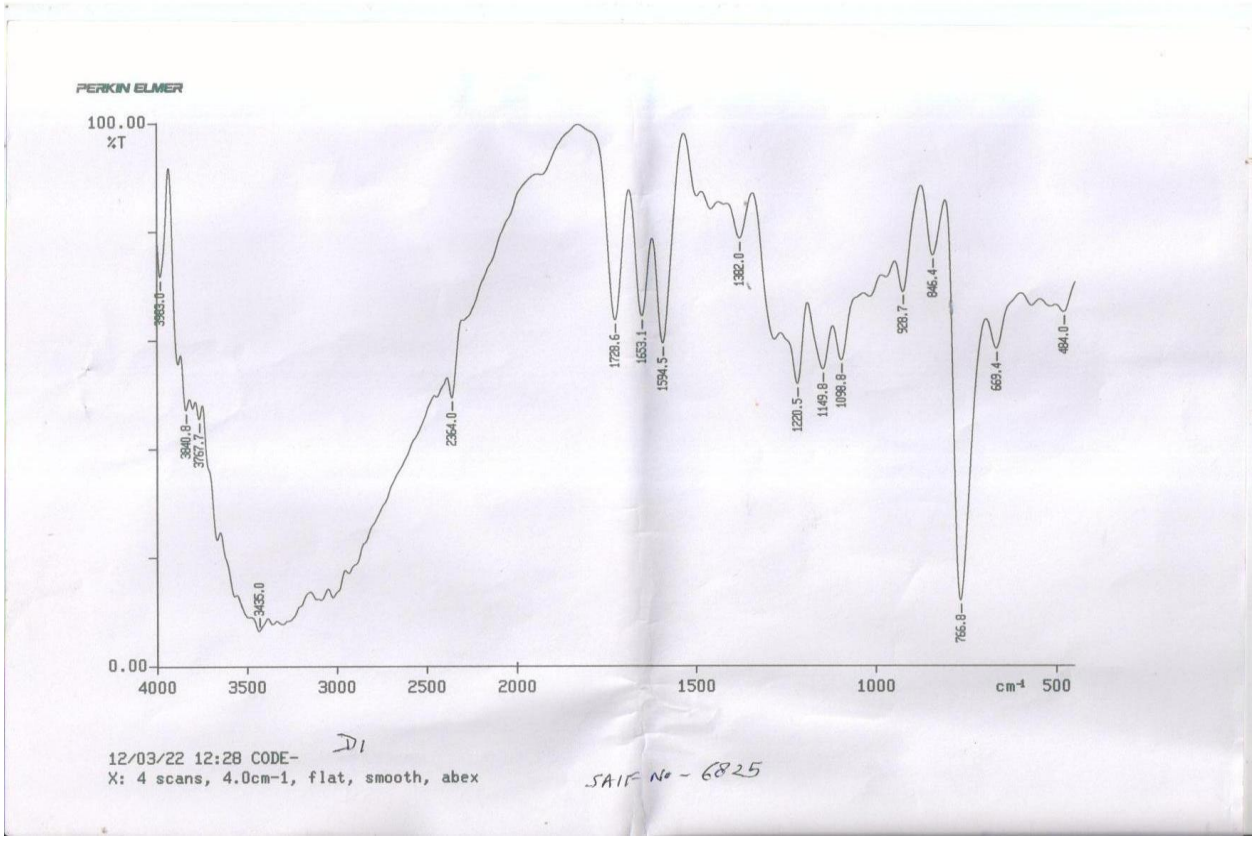


Fig no 2.1:-Infrared analysis of Fenofibrate

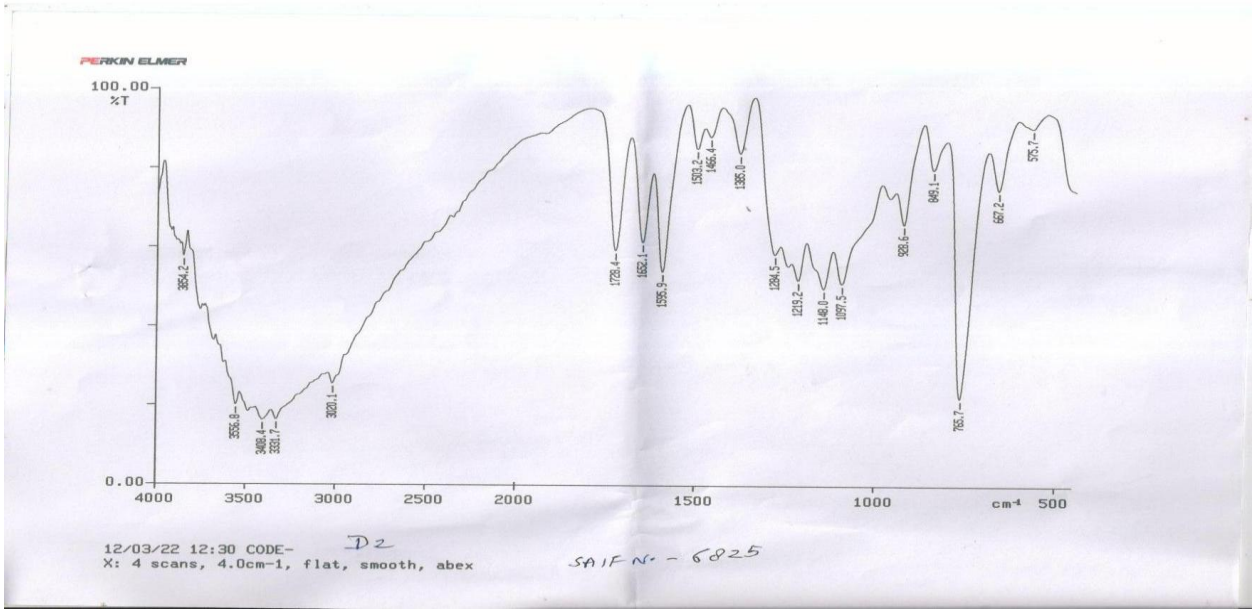


Fig no 2.2-Infrared analysis of Fenofibrate with Microcrystalline cellulose

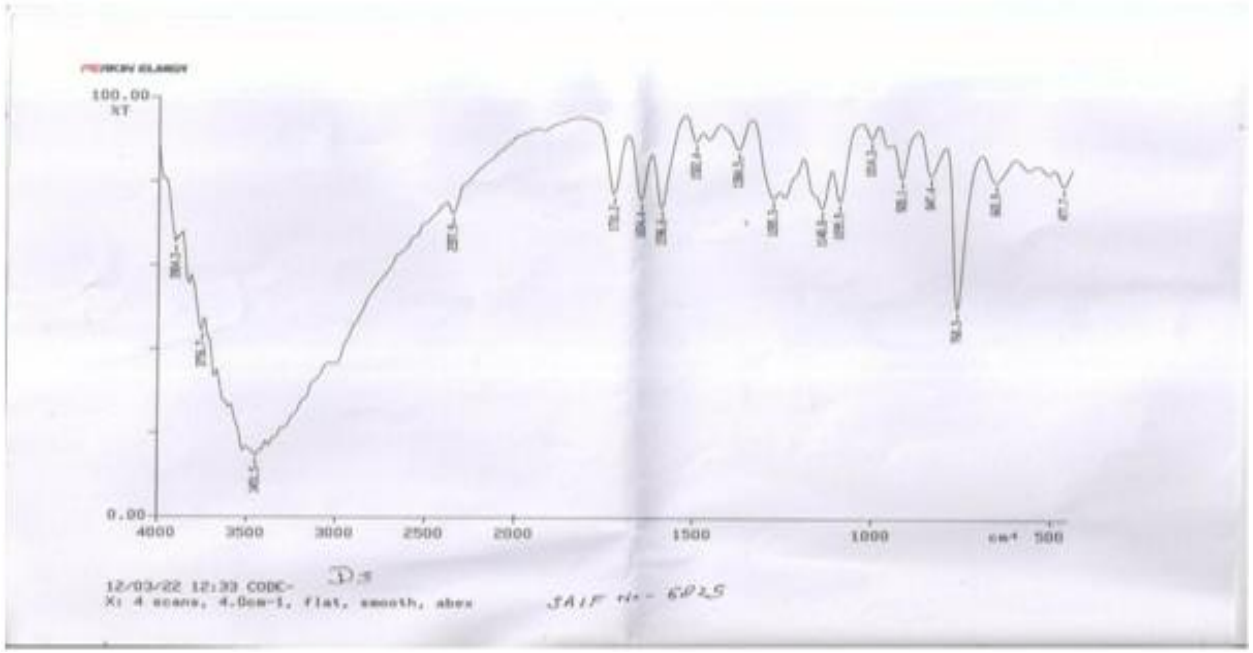


Fig no 2.3 -Infrared analysis of Fenofibrate with silica

Table no 2.7- IR interpretation of Fenofibrate :-

TYPE	NATURE	WAVE NUMBER
Aromatic C-H bond	Sharp, Strong	3435 cm^{-1}
C-H bond	Weak	2364 cm^{-1}
Carbonyl group	Sharp, Strong	1728 cm^{-1}
C-H stretching	Medium	1098 cm^{-1}
Aromatic ring	Medium	846.4 cm^{-1}
C-Cl stretching	Sharp, Strong	766.8 cm^{-1}
O-H stretching	Weak	3767.7 cm^{-1}

Table no 2.8:-Infrared analysis of Fenofibrate with Microcrystalline cellulose:-

TYPE	NATURE	WAVE NUMBER
Aromatic C-H bond	Sharp, Strong	3435 cm^{-1}
C-H bond	Weak	2364 cm^{-1}
Carbonyl group	Sharp, Strong	1728 cm^{-1}
C-H stretching	Medium	1098 cm^{-1}
Aromatic ring	Medium	846.4 cm^{-1}
C-Cl stretching	Sharp, Strong	766.8 cm^{-1}
O-H stretching	Weak	3767.7 cm^{-1}

Table no 2.9-Infrared analysis of Fenofibrate with Microcrystalline cellulose:-

TYPE	NATURE	WAVE NUMBER
Aromatic C-H bond	Sharp, Strong	3451.5 cm^{-1}
C-H bond	Weak	2357.9 cm^{-1}
Carbonyl group	Sharp, Strong	1731.2 cm^{-1}
C-H stretching	Medium	1099.9 cm^{-1}
Aromatic ring	Medium	847.4 cm^{-1}
C-Cl stretching	Sharp, Strong	768.3 cm^{-1}
O-H stretching	Weak	3756.7 cm^{-1}

From the IR spectra of Drug(Fenofibrate) and excipients (Mcc and silica) it can be concluded that there is no interaction between drug excipient mixture.

CHAPTER-3
FORMULATION & EVALUATION

Fenofibrate tablets were prepared by Liquisolid technique. Fifteen batches were prepared with following process variables :-

1-Concentration of drug in non-volatile solvent.

2-Powder-excipient ratios.

3-Ratios of carrier and coating material.

4-Types of non-volatile solvents

EVALUATION

Prepared liquisolid tablets were evaluated for the following parameters :-

1-Weight variation

2-Uniformity of tablet thickness

3-Content uniformity

4- Friability

5-Hardness

6-Humidity content

7-Disintegration test

8-Dissolution studies of Liquisolid tablet

Formulation of Fenofibrate tablets using Liquisolid technique :-

1. Fenofibrate was initially dispersed in the nonvolatile solvent systems (Polyethylene glycol-400) termed as liquid vehicles with different drug: vehicle ratios. This non-volatile solvent with

drug dissolved may be existing in solution or else suspension nature known as “liquid medicament”.

2. Then a mixture of carrier (Microcrystalline cellulose) and coating material (silica) were added to the above liquid medication under continuous mixing in a mortar. These amounts of the carrier and coating material are enough to maintain acceptable flow and compression properties.

3. To the above binary mixture disintegrant like sodium starch glycolate and other reaming additives like binder (starch) were added according to their application and mixed for a period of 10 to 20 min. in a mortar.

4. The final mixture was compressed using the manual tableting machine to achieve tablet hardness.

5. Characterize the final liquisolid granules for solubility, dissolution, flowability, compressibility and other physicochemical properties.[82]

Flowchart[84]:- **DRUG(FENOFIBRATE)**

↓

ADD NON VOLATILE SOLVENT (PEG 400)

↓

CARRIER MATERIAL(MICROCRYSTALLINE CELLULOSE)

↓

COATING MATERIAL (SILICA)

↓

THEN ADD DISINTEDRANT (SODIUM STARCH GLYCOLATE)

↓

BINDER (STARCH)

Design and formulation of this approach is prescribed according to new mathematical model. Increasing the solubility by using a non-volatile solvent which is suitable for drug, their by dissolving the drug in the non volatile solvent and this is termed as liquid medicament . Blending the liquid medicament with mixture of carrier and coating material, liquid medicament can be converted into non adhere, dry looking powder with acceptable flow properties and compression behavior using suitable excipients and tabletting by direct compression method. The drug release rates of Liquisolid compacts were distinctly higher as compared to directly compressed tablets, which show significant benefit of Liquisolid technique in increasing wetting properties and surface area of drug available for dissolution.

Table no.3.1-Formulation of liquisolid Fenofibrate tablets:-

S.NO (BATCHES)	Fenofibrate Conc in PEG 400	R (Excipient ratio)	Lf (Loading factor)	Q=W/Lf (Carrier) mg	q=Q/R (coating material) gm	Unit dose (gm)
LS-1.	10%	10	0.491	1.11	0.112	1.22
LS-2.	10%	20	0.326	1.23	0.240	1.25
LS-3.	10%	30	0.270	1.34	0.323	1.28
LS-4.	10%	40	0.243	1.16	0.367	1.31
LS-5.	20%	10	0.491	1.24	0.234	1.25
LS-6.	20%	20	0.326	1.25	0.256	1.27
LS-7.	20%	30	0.270	1.34	0.267	1.29
LS-8.	20%	40	0.243	1.34	0.345	1.32
LS-9.	30%	100	0.491	1.20	0.258	1.26
LS-10	30%	020	0.326	1.27	0.261	1.27
LS-11.	30%	30	0.270	1.28	0.276	1.28
LS-12.	30%	40	0.243	1.36	0.321	1.33
LS-13.	40%	10	0.491	1.32	0.342	1.27
LS-14.	40%	20	0.326	1.34	0.346	1.28
LS-15.	40%	30	0.270	1.38	0.356	1.34
LS-16.	40%	40	0.243	1.39	0.359	1.35

It was observable that batch no 2nd,5th,6th,8th,9th,11th complied with the test.so only these batches were evaluated for following parameters:-

Evaluation of Fenofibrate tablets :-

a-Weight variation

10 tablets were randomly selected from the prepared batches and their average weight was calculated using a digital balance. Individual weight of each tablet was also determined and compared with the average weight.[85]

b-Uniformity of tablet thickness

Vernier caliper was used to determine the thickness of the prepared tablets. 10 tablets were randomly selected from each trial batch and were measured by placing the tablet between the anvils and sliding knob was rotated until the tablet was ruptured.[86]

After the test it was found that no tablet was ruptured , each tablet was equally thick.

c-Content uniformity

For content uniformity test tablets should contain not less than 95% and not more than 105% of the labeled potency .

After the test it was found that the contents of each tablet were uniform.The amount of each excipient is same in each tablet.[87]

d- Friability

The friability test is closely related to tablet hardness and is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. Measured by the use of the Roche friabilator .

Method:

(i) A number of tablets (6 tablets) are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus.

(ii) After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability.

(iii) The value is expressed as a percentage.

(iv) A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked up.[88]

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

Maximum weight loss=Less than 1%

e-Hardness

Hardness or crushing strength determinations are made during tablet production, are used to determine the need for pressure adjustment on tablet machine. The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets The Monsanto or Stokes hardness tester. The Strong-Cobb apparatus. Schleuniger apparatus.

Oral tablets have 4 to 10 kg hardness. hypodermic and chewable tablets are usually much softer (3 kg) and some sustained release tablets are much harder (10-20 kg). Tablet hardness have been associated ith other tablet properties such as density and porosity.[89]

Hardness of Fenofibrate tablets = 7 Kg/ mt^2

f-Disintegration test

Disintegration for a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration. The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 mesh screen.

The disintegration test is carried out using the disintegration tester which consists of a basket rack holding 6 plastic tubes, open at the top and bottom, the bottom of the tube is covered by a 10-mesh screen. The basket is immersed in a bath of suitable liquid held at 37 O C, preferably in a 1L beaker. For most uncoated tablets, the BP requires that the tablets disintegrate in 15 minutes

(although it varies for some uncoated tablets) while for coated tablets, up to 2 hours may be required.

To test for disintegration time, one tablet is placed in each test tube & basket rack is positioned in a 1L beaker of water, simulated gastric fluid at 37 o C ± 2 o C, such that tablets remain 2.5 cm below the surface of liquid on their upward movement. A standard motor driven device is used to move the basket assembly, at a frequency of 28-32 cycles/min. To be in USP standards, tablet must disintegrate & all particles must pass through 10 mesh screen in specified time.[90]

Table no 3.2.- Avg fenofibrate content, % friability ,Hardness , Disintigration time of Fenofibrate:-

Batch no	**Avg fenofibrate content**	**% friability**	**Hardness (kg/mt^2)**	**Disintigration time(min)**
LS-2	94%	0.046	6	12
LS-5.	94.62%	0.043	6.2	11
LS-6	96%	0.067	6	14
LS-8.	98.56%	0.087	6.6	10
LS-9	97%	0.048	6.3	11
LS-11.	99%	0.039	6.9	13

g-Humdity content

Humidity means presence of water or moisture in tablet. It decreases the bioavailability and efficacy of drug . 1 tablet is placed in petridish and allowed to stand for 2-3 hours at 25 ^{0}c.It should not be more than ± .5% . It can be calculated by the following formula:-

% Humidity= Increase in wt/ Initial wt of tablet x 100

Table no 3.3 -% Humidity of Fenofibrate:-

Batch no	Initial wt of tablet(mg)	Wt of tablet After 2 hours (mg)	Increase in wt (mg)	% Humidity
LS-2.	1250	1251.3	1.3	0.104
LS-5.	1230	1231.4	1.4	0.113
LS-6	1250	1251.4	1,4	0.113
LS-8.	1220	1221.6	1.6	0.131
LS-9	1260	1262.0	2.0	0.158
LS-11.	1280	1282.5	2.5	0.195

h- Dissolution studies of Liquisolid tablet

Dissolution is the process by which a solid solute enters a solution. Pharmaceutically, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. Dissolution kinetics is important in determining the bioavailability of a drug

.

Dissolution can be carried out in (i) USP dissolution apparatus Type I (Basket type). (ii) USP dissolution apparatus Type II (Paddle type). In general, a single tablet is placed in a small wire mesh basket fastened to the bottom of the shaft connected to a variable speed motor. The basket is immersed in the dissolution medium (PBS 7.4) contained in a flask. The flask is maintained at constant temperature of 37 o C ± 5 o C by a constant temperature bath.[91]

Table no 3.4 – % drug release of Batch no 2-

S.no	Time (min)	Absorbance	Conc	Y-Intercept	X=Y-Intercept/slope	X x Dilution factor(10)	Amount of drug in 900 ml(µg/ml)	Amount in drug in mg	%drug release
LS- 1	0	0	0	0	0	0	0	0	0
LS-2	60	0.016	0.01548	0.377837	3.778374	3400.537	3.400537	0.340054	34.00537
LS-3	120	0.0181	0.01758	0.429094	4.290945	3861.85	3.86185	0.386185	38.6185
LS-4	180	0.0188	0.01828	0.44618	4.461801	4015.621	4.015621	0.401562	40.15621
LS-5	240	0.019	0.01848	0.451062	4.510618	4059.556	4.059556	0.405956	40.59556
LS-6	300	0.0197	0.01918	0.468147	4.681474	4213.327	4.213327	0.421333	42.13327
LS-7	360	0.021	0.02048	0.499878	4.99878	4498.902	4.498902	0.44989	44.98902
LS-8	420	0.0253	0.02478	0.604833	6.048328	5443.495	5.443495	0.54435	54.43495
LS-9	480	0.0254	0.02488	0.607274	6.072736	5465.463	5.465463	0.546546	54.65463

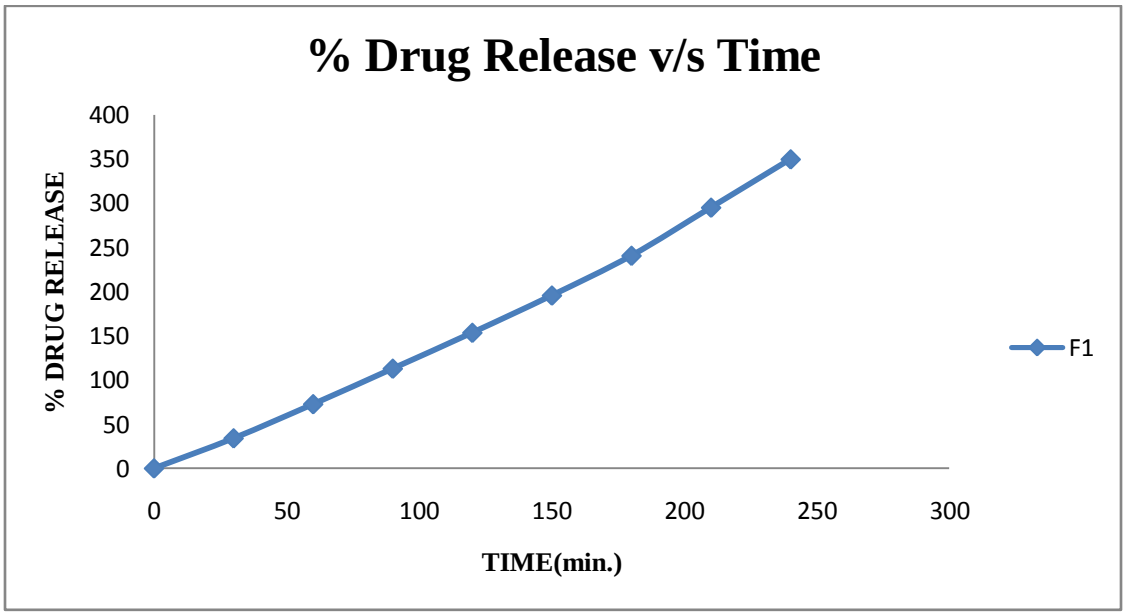


Fig no 3.1 In vitro release profile of batch no 2

Table no 3.5 - % drug release of Batch no 5-

S.no	Time (min)	Absorbance	Conc	Y-Intercept	X=Y-Intercept/slope	X x Dilution factor(10)	Amount of drug in 900 ml(µg/ml)	Amount in drug in mg	%drug release
LS-1	0	0	0	0	0	0	0	0	0
LS-2	60	0.0178	0.01728	0.421772	4.21772	3795.948	3.795948	0.379595	37.95948
LS-3	120	0.0189	0.01838	0.448621	4.486209	4037.588	4.037588	0.403759	40.37588
LS-4	180	0.0198	0.01928	0.470588	4.705882	4235.294	4.235294	0.423529	42.35294
LS-5	240	0.021	0.02048	0.499878	4.99878	4498.902	4.498902	0.44989	44.98902
LS-6	300	0.024	0.02348	0.573102	5.731023	5157.92	5.15792	0.515792	51.5792
LS-7	360	0.027	0.02648	0.646327	6.463266	5816.939	5.816939	0.581694	58.16939
LS-8	420	0.029	0.02848	0.695143	6.951428	6256.285	6.256285	0.625629	62.56285
LS-9	480	0.029	0.03148	0.768367	7.683671	6915.304	6.915304	0.69153	69.15304

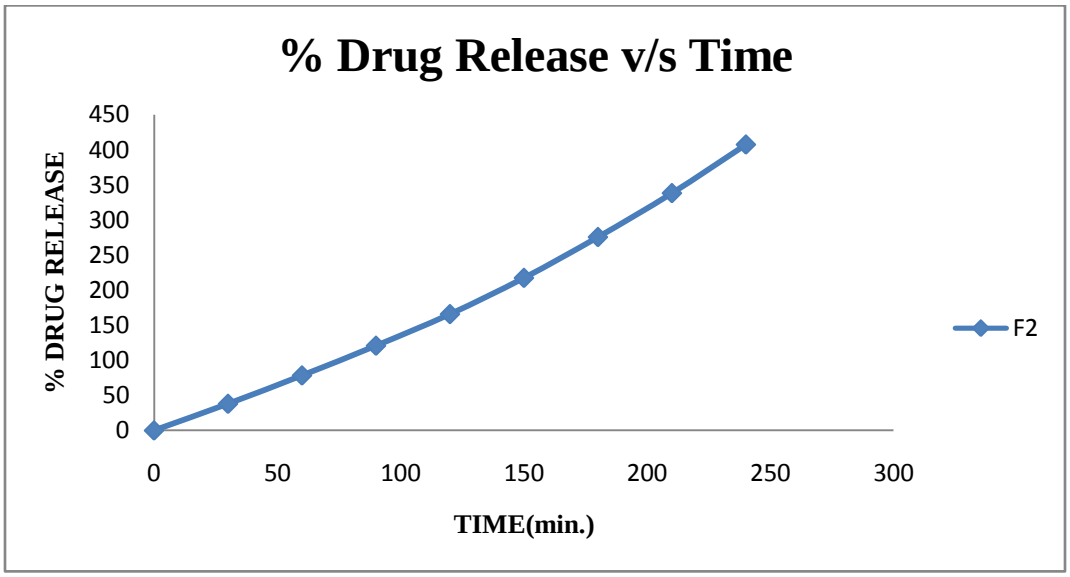


Fig no 3.2 -In vitro release profile of batch no 5

Table no 3.6– % drug release of Batch no 6-

S.no	Time (min)	Absorbance	Conc	Y-Intercept	X=Y-Intercept/slope	X x Dilution factor(10)	Amount of drug in 900 ml(µg/ml)	Amount in drug in mg	%drug release
LS-1	0	0	0	0	0	0	0	0	0
LS-2	60	0.0212	0.02068	0.50476	5.047596	4542.836	4.542836	0.454284	45.42836
LS-3	120	0.0215	0.02098	0.512082	5.12082	4608.738	4.608738	0.460874	46.08738
LS-4	180	0.0221	0.02158	0.526727	5.267269	4740.542	4.740542	0.474054	47.40542
LS-5	240	0.0225	0.02198	0.53649	5.364901	4828.411	4.828411	0.482841	48.28411
LS-6	300	0.0256	0.02508	0.612155	6.121552	5509.397	5.509397	0.55094	55.09397
LS-7	360	0.0269	0.02638	0.643886	6.438858	5794.972	5.794972	0.579497	57.94972
LS-8	420	0.0289	0.02838	0.692702	6.92702	6234.318	6.234318	0.623432	62.34318
LS-9	480	0.0290	0.02868	0.700024	7.000244	6300.22	6.30022	0.630022	63.0022

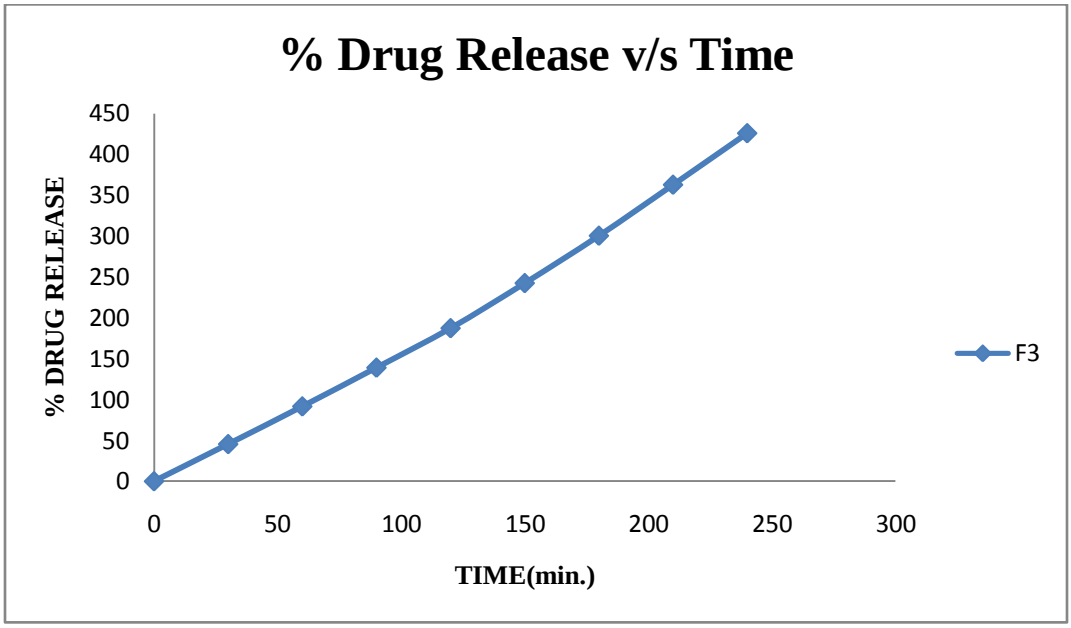


Fig no 3.3 In vitro release profile of batch no 6

Table no 3.7 – % drug release of Batch no 8-

S.no	Time (min)	Absorbance	Conc	Y-Intercept	X=Y-Intercept/slope	X x Dilution factor(10)	Amount of drug in 900 ml(µg/ml)	Amount in drug in mg	%drug release
LS-1	0	0	0	0	0	0	0	0	0
LS-2	60	0.018	0.01748	0.426654	4.266536	3839.883	3.839883	0.383988	38.39883
LS-3	120	0.0187	0.01818	0.443739	4.437393	3993.654	3.993654	0.399365	39.93654
LS-4	180	0.0191	0.01858	0.453503	4.535026	4081.523	4.081523	0.408152	40.81523
LS-5	240	0.021	0.02048	0.499878	4.99878	4498.902	4.498902	0.44989	44.98902
LS-6	300	0.022	0.02148	0.524286	5.242861	4718.575	4.718575	0.471857	47.18575
LS-7	360	0.0241	0.02358	0.575543	5.755431	5179.888	5.179888	0.517989	51.79888
LS-8	420	0.0261	0.02558	0.624359	6.243593	5619.234	5.619234	0.561923	56.19234
LS-9	480	0.0282	0.02768	0.675616	6.756163	6080.547	6.080547	0.608055	60.80547

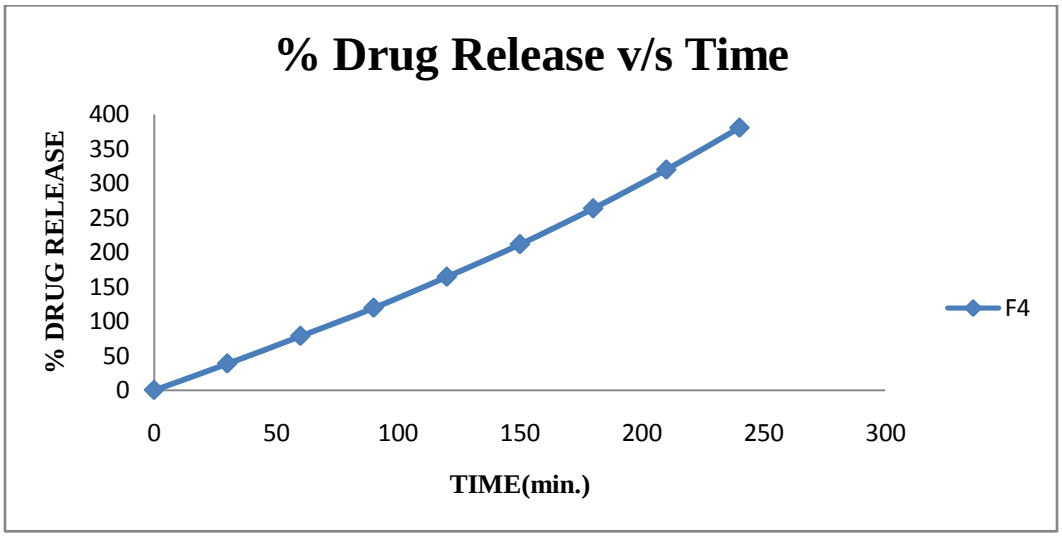


Fig no 3.4 In vitro release profile of batch no 8

Table no 3.8 - % drug release of Batch no 9-

S.no	Time (min)	Absorbance	Conc	Y-Intercept	X=Y-Intercept/slope	X x Dilution factor(10)	Amount of drug in 900 ml(µg/ml)	Amount in drug in mg	%drug release
LS-1	0	0	0	0	0	0	0	0	0
LS-2	60	0.0189	0.01838	0.448621	4.486209	4037.588	4.037588	0.403759	40.37588
LS-3	120	0.0198	0.01928	0.470588	4.705882	4235.294	4.235294	0.423529	42.35294
LS--4	180	0.0238	0.02328	0.568221	5.682206	5113.986	5.113986	0.511399	51.13986
LS-5	240	0.0298	0.02928	0.714669	7.146693	6432.023	6.432023	0.643202	64.32023
LS-6	300	0.03	0.02948	0.719551	7.195509	6475.958	6.475958	0.647596	64.75958
LS-7	360	0.0378	0.03728	0.909934	9.099341	8189.407	8.189407	0.818941	81.89407
LS-8	420	0.0378	0.03728	0.909934	9.099341	8189.407	8.189407	0.818941	81.89407
LS--9	480	0.0379	0.03738	0.912375	9.123749	8211.374	8.211374	0.821137	82.11374

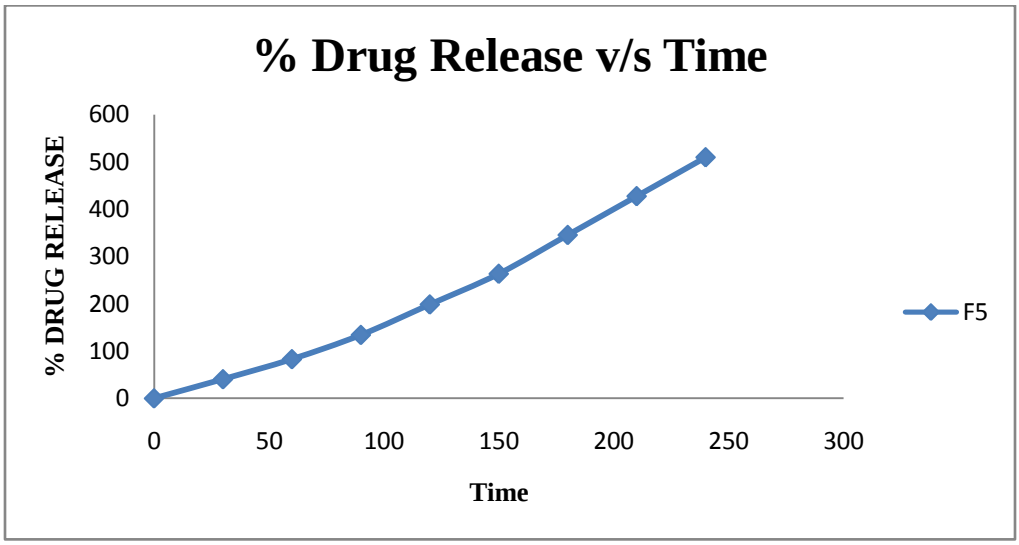


Fig no 3.5- In vitro release profile of batch no 9

Table no 3.9 - % drug release of Batch no 11-

S.no	Time (min)	Absorbance	Conc	Y-Intercept	X=Y-Intercept/slope	X x Dilution factor(10)	Amount of drug in 900 ml(µg/ml)	Amount in drug in mg	% drug release
LS-1	0	0	0	0	0	0	0	0	0
LS-2	60	0.0189	0.01838	0.448621	4.486209	4037.588	4.037588	0.403759	40.37588
LS-3	120	0.0199	0.01938	0.473029	4.73029	4257.261	4.257261	0.425726	42.57261
LS-4	180	0.0267	0.02618	0.639004	6.390041	5751.037	5.751037	0.575104	57.51037
LS-5	240	0.0287	0.02818	0.68782	6.878204	6190.383	6.190383	0.619038	61.90383
LS-6	300	0.0297	0.02918	0.712228	7.122285	6410.056	6.410056	0.641006	64.10056
LS-7	360	0.0347	0.03418	0.834269	8.34269	7508.421	7.508421	0.750842	75.08421
LS-8	420	0.0367	0.03618	0.883085	8.830852	7947.767	7.947767	0.794777	79.47767
LS-9	480	0.0368	0.03628	0.885526	8.85526	7969.734	7.969734	0.796973	79.69734

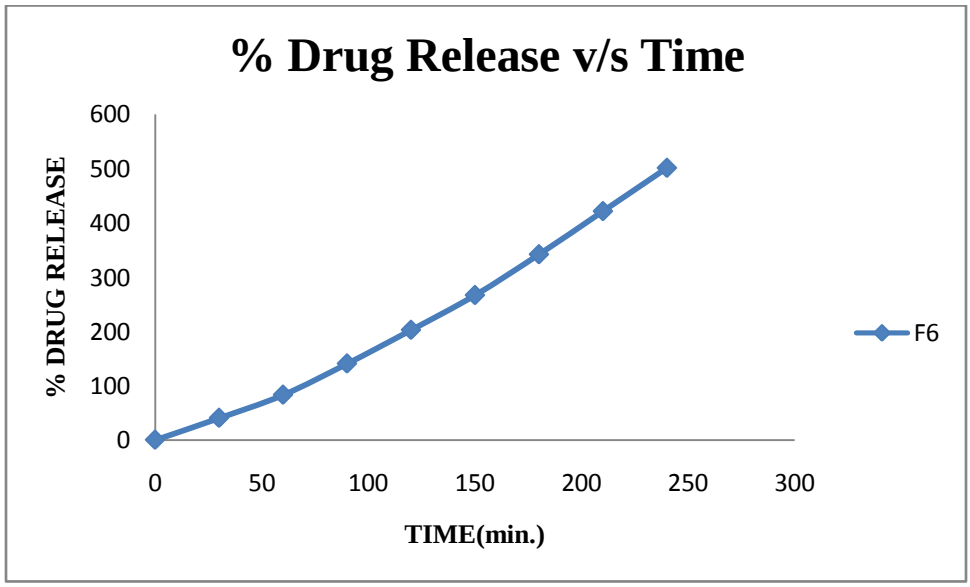


Fig no 3.6- In vitro release profile of batch no 11

Table no 3.10 – % drug release of all the Batches (Combined table):-

s.no	time (min)	2nd batch	5th batch	6th batch	8th batch	9th batch	11th batch
LS-1	0	0	0	0	0	0	0
LS-2	60	34.00537	37.95948	45.42836	38.39883	32.24799	35.76275
LS-3	120	72.62387	78.33537	91.51574	78.33537	67.79107	74.60093
LS-4	180	112.7801	120.6883	138.9212	119.1506	103.7955	116.9539
LS-5	240	153.3756	165.6773	187.2053	164.1396	140.4369	166.3363
LS-6	300	195.5089	217.2565	242.2992	211.3254	180.8128	226.7025
LS-7	360	240.4979	275.4259	300.249	263.1242	223.3854	289.2653
LS-8	420	294.9329	337.9888	362.5921	319.3166	274.5253	356.8806
LS-9	480	349.5875	407.1418	425.5943	380.122	330.2783	424.7156

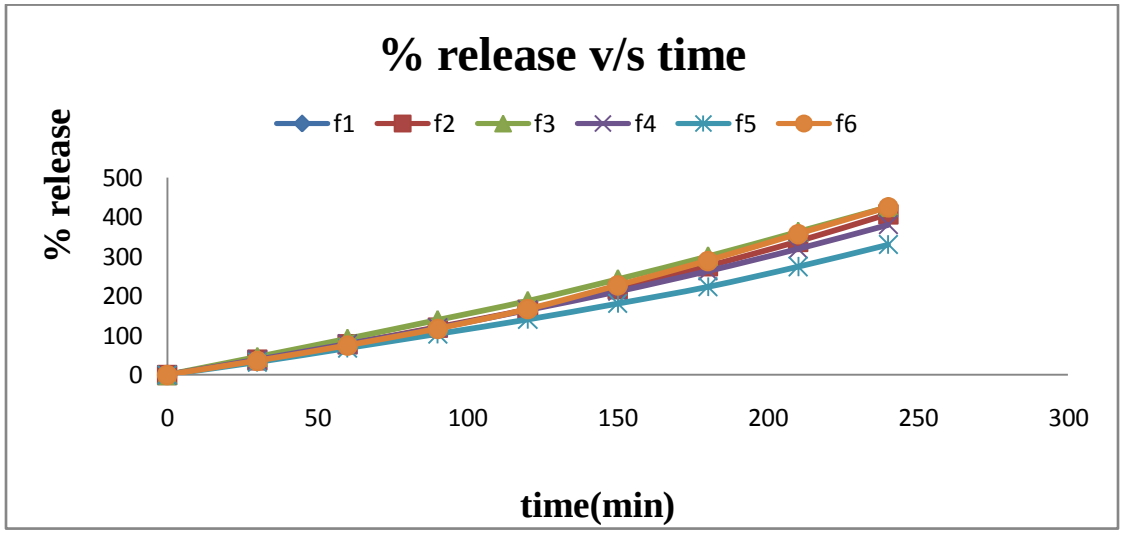


Fig no 3.7- In vitro release profile of all the batches

Table no 3.11 - % Drug release of Conventional Direct Compression Tablet :-

S.no	Time (min)	Absorbance	Conc	Y-Intercept	X=Y-Intercept/slope	X x Dilution factor(10)	Amount of drug in 900 ml(µg/ml)	Amount in drug in mg	%drug release
LS-1	0	0	0	0	0	0	0	0	0
LS-2	60	0.012	0.01148	0.280205	2.80205	2521.845	2.521845	0.252185	25.21845
LS-3	120	0.0135	0.01298	0.316817	3.168172	2851.355	2.851355	0.285135	28.51355
LS-4	180	0.0155	0.01498	0.365633	3.656334	3290.701	3.290701	0.32907	32.90701
LS-5	240	0.0175	0.01698	0.41445	4.144496	3730.046	3.730046	0.373005	37.30046
LS-6	300	0.0188	0.01828	0.44618	4.461801	4015.621	4.015621	0.401562	40.15621
LS-7	360	0.0197	0.01918	0.468147	4.681474	4213.327	4.213327	0.421333	42.13327
LS-8	420	0.021	0.02048	0.499878	4.99878	4498.902	4.498902	0.44989	44.98902
LS-9	480	0.0253	0.02478	0.604833	6.048328	5443.495	5.443495	0.54435	54.43495

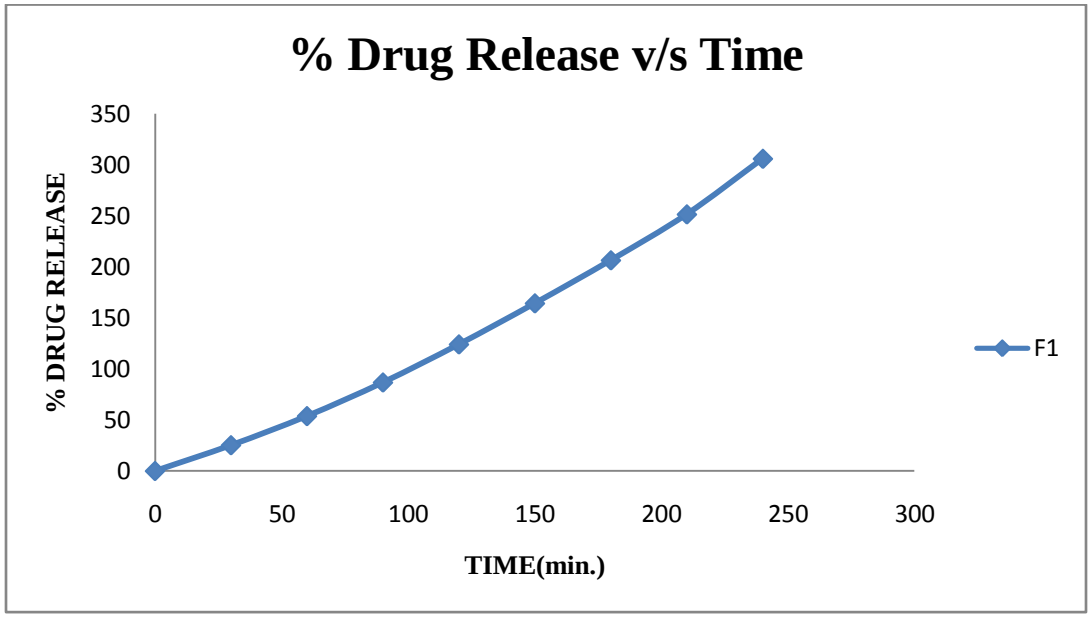


Fig no 3.8- In vitro release profile of conventional DCT

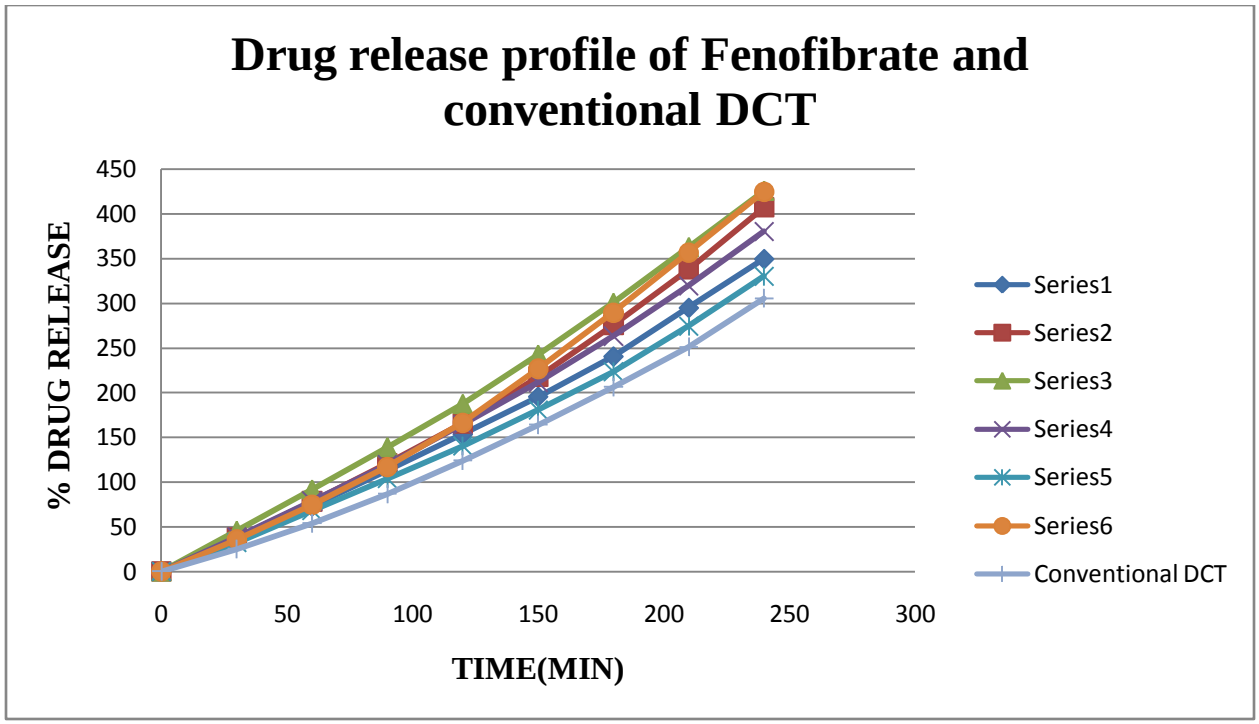


Fig no 3.9 - Dissolution profile of fenofibrate from the liquisolid tablet systems & the conventional DCT

Table no 3.12 - % Drug release of Marketed Preparation:-

S.no	Time (min)	Absorbance	Conc	Y-Intercept	X=Y-Intercept/slope	X x Dilution factor(10)	Amount of drug in 900 ml(µg/ml)	Amount in drug in mg	%drug release
LS-1	0	0	0	0	0	0	0	0	0
LS-2	60	0.012	0.01148	0.280205	2.80205	2521.845	2.521845	0.252185	35.21845
LS-3	120	0.0135	0.01298	0.316817	3.168172	2851.355	2.851355	0.285135	47.51355
LS-4	180	0.0155	0.01498	0.365633	3.656334	3290.701	3.290701	0.32907	58.90701
LS-5	240	0.0175	0.01698	0.41445	4.144496	3730.046	3.730046	0.373005	60.30046
LS-6	300	0.0188	0.01828	0.44618	4.461801	4015.621	4.015621	0.401562	67.15621
LS-7	360	0.0197	0.01918	0.468147	4.681474	4213.327	4.213327	0.421333	75.13327
LS-8	420	0.021	0.02048	0.499878	4.99878	4498.902	4.498902	0.44989	79.98902
LS-9	480	0.0253	0.02478	0.604833	6.048328	5443.495	5.443495	0.54435	82.43495

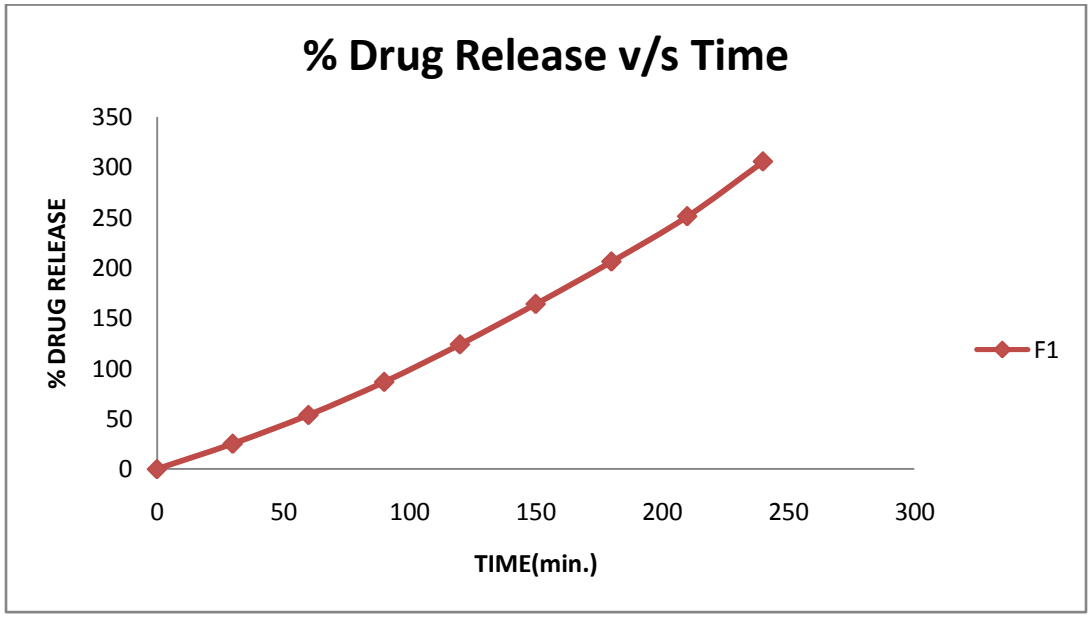


Fig no 3.10- In vitro release profile of conventional Marketed Preparation

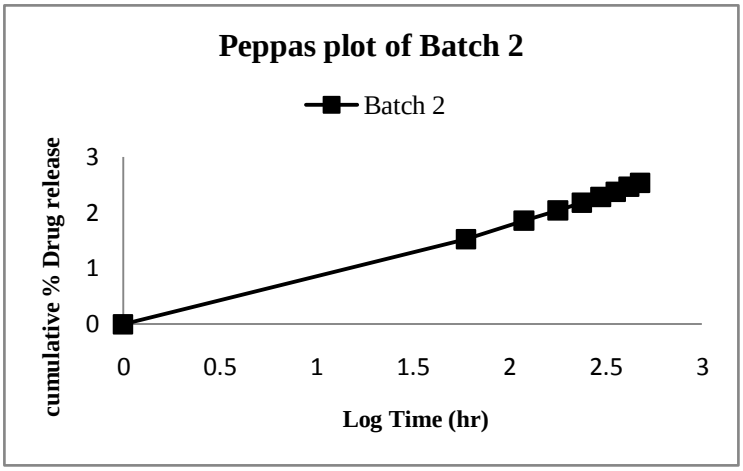
TABLE NO 3.13 - KINETICS OF DRUG RELEASE (Liquisolid tablets of Fenofibrate):-

S.NO	kinetic parameter	Batch no-2		Batch no-5		Batch no-6		Batch no-8		Batch no-9		Batch no-11	
1		R	K	R	K	R	K	R	K	R	K	R	K
2	ZeroOrder	0.7928	10.1212	0.7598	10.8505	0.6993	12.7488	0.7308	10.5996	0.8527	12.6262	0.9088	13.6970
3	T-test	1.840	(Passes)	1.653	(Passes)	1.384	(passes)	1.514	(Passes)	2.309	(passes)	3.081	(passes)
4	FirstOrder	0.8081	0.1156	0.7740	0.1252	0.7077	0.1514	0.7413	0.1218	0.8784	0.1502	0.9336	0.1668
5	T-test	1.940	(Passes)	1.729	(Passes)	1.417	(passes	1.562	(passes)	2.599	(passes)	3.684	(passes)
6	Matrix	0.9625	16.0950	0.9494	17.3160	0.9241	20.4687	0.9381	16.9689	0.9767	19.8947	0.9826	21.3446
7	T-test	5.017	(Passes)	4.274	(Passes)	3.419	(passes)	3.829	(passes)	6.432	(Passes)	7.481	(Passes)
8	Peppas	0.9873	20.5451	0.9982	22.9841	0.8989	28.6889	0.9965	23.0873	0.8896	24.0744	0.8640	23.6129
9	T-test	8.797	(Passes)	23.385	(Passes)	2.901	(passes)	16.943	(Passes)	2.755	(passes)	2.427	(passes)
10	Hix crow	0.8030	0.0368	0.7692	0.0398	0.7048	0.0467	0.7377	0.0387	0.8699	0.0472	0.9260	0.0520
11	T-test	1.905	(Passes)	1.702	(Passes)	1.405	(passes)	1.545	(passes)	2.495	(passes)	3.469	(passes)
12	Best fit model	Peppas n=0.1767,k=20.5451		Peppas n=0.1221,k=22.9841		Matrix n=0.0453,k=28.6889		Peppas n=0.0877,k=23.0873		Matrixs n=0.2442,k=24.0744		Matrixs n=0.3570,k=23.6129	

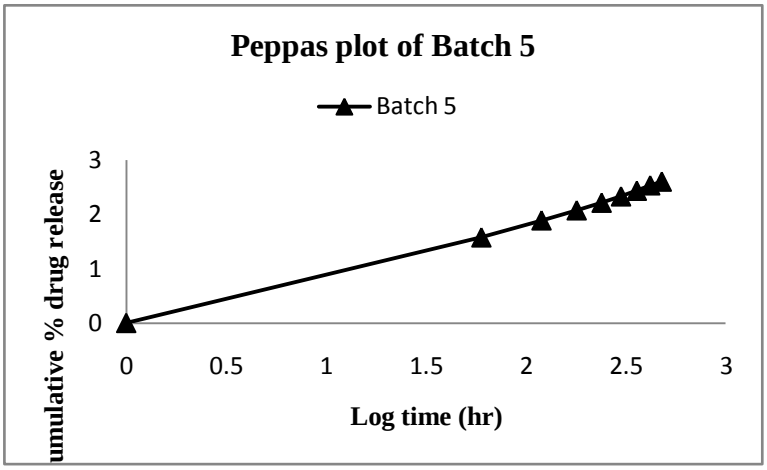
TABLE NO 3.14 - KINETICS OF DRUG RELEASE (Conventional DCT):-

S.NO	kinetic parameter	Batch no-2	
1		R	K
2	ZeroOrder	0.8782	7.3495
3	T-test	2.597	(passes)
4	FirstOrder	0.8921	0.0808
5	T-test	2.793	(passes)
6	Matrix	0.9871	11.5436
7	T-test	8.720	(Passes)
8	Peppas	0.9659	13.4217
9	T-test	5.278	(Passes)
10	Hix crow	0.8875	0.0261
11	T-test	2.724	(passes)
12	Best fit model	Matricx(n=0.3000,k=13.4217)	

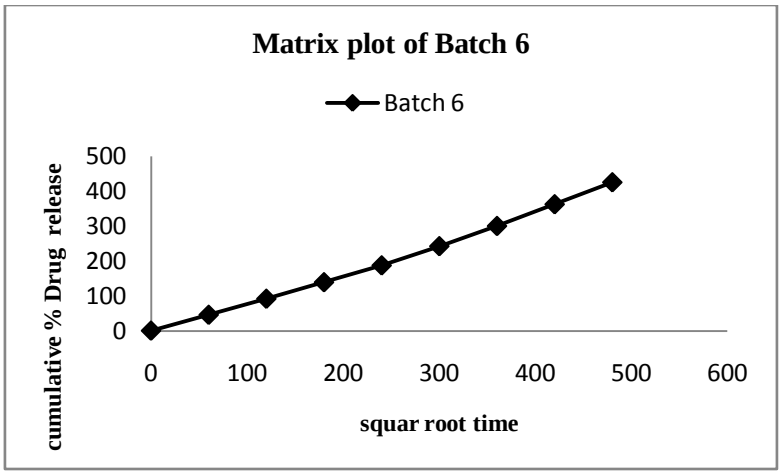
S.no	Log Time	%Drug release
1	0	0
2	1.778	1.531
3	2.079	1.861
4	2.255	2.052
5	2.38	2.184
6	2.477	2.291
7	2.556	2.381
8	2.623	2.469
9	2.681	2.542



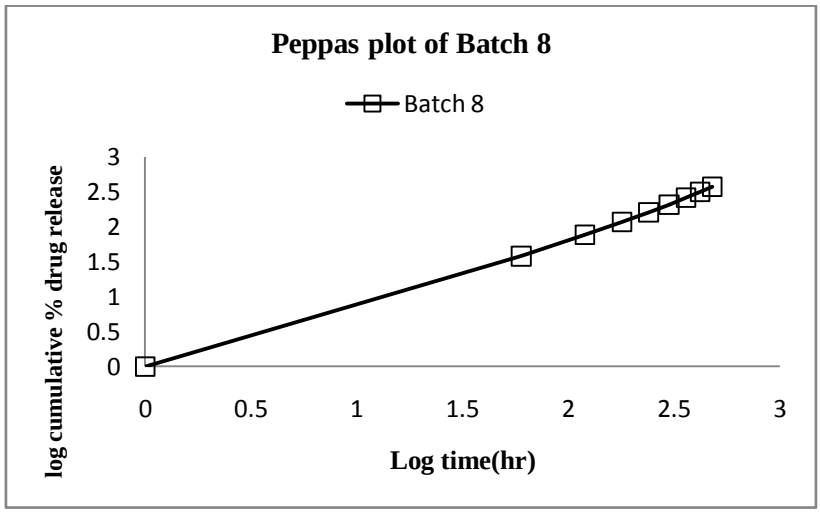
S.no	Log Time	%Drug release
1	0	0
2	1.778	1.579
3	2.079	1.893
4	2.255	2.079
5	2.38	2.219
6	2.477	2.336
7	2.556	2.440
8	2.623	2.28
9	2.681	2.609



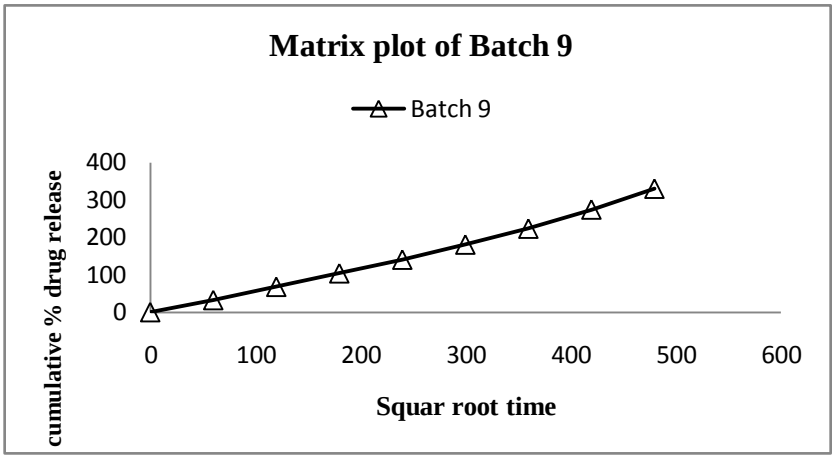
S.no	Squar Root time	%Drug release
1	0	0
2	60	45.42836
3	120	91.51574
4	180	138.9212
5	240	187.2053
6	300	242.2992
7	360	300.249
8	420	362.5921
9	480	425.5943



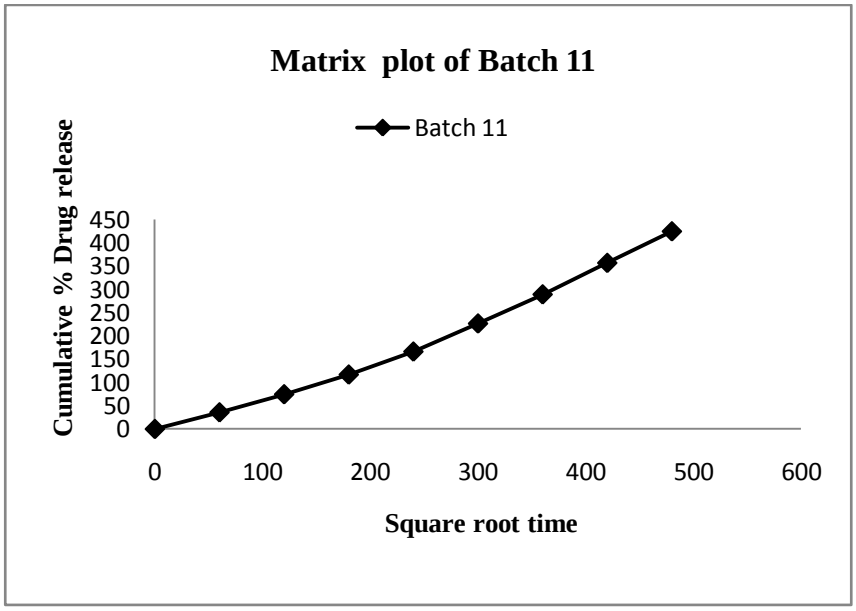
S.no	Log time	%Drug release
1	0	0
2	1.778	1.584
3	2.079	1.893
4	2.255	2.076
5	2.38	2.215
6	2.477	2.324
7	2.556	2.420
8	2.623	2.504
9	2.681	2.579



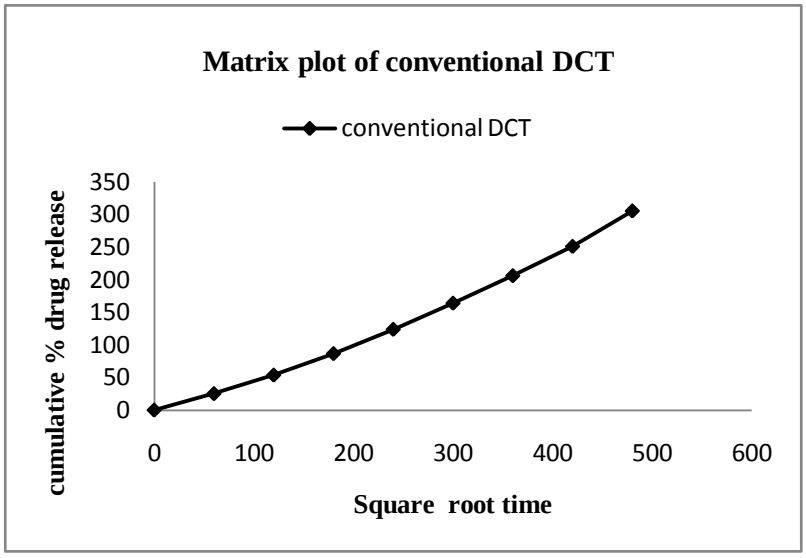
S.no	Squar Root time	%Drug release
1	0	0
2	60	32.24799
3	120	67.79107
4	180	103.7955
5	240	140.4369
6	300	180.8128
7	360	223.3854
8	420	274.5253
9	480	330.2783



S.no	Squar Root time	%Drug release
1	0	0
2	60	35.76275
3	120	74.60093
4	180	116.9539
5	240	166.3363
6	300	226.7025
7	360	289.2653
8	420	356.8806
9	480	424.7156



S.no	Squar Root time	%Drug release
1	0	0
2	60	25.21845
3	120	53.732
4	180	86.639
5	240	123.9395
6	300	164.0957
7	360	206.2289
8	420	251.218
9	480	305.6529



CHAPTER-4
RESULT & DISCUSSION

4.1 Tablet Hardness:

Hardness of the developed formulations varied from 6.0 to 6.9 kg/cm2 (Table 3.1) in all the formulation indicating good mechanical strength with an ability to withstand physical and mechanical stress condition while handling. The batches LS-2, LS-5, LS-6, LS-8, LS-9, LS- 11 showed best results neither it was too hard or too soft, while the rest of the batches containing less concentration of binder were comparatively softer and those that had high concentration were very hard.

4.2 Friability:

The loss in total weight of the tablets due to friability was in the range of 0.039% to 0.087% (Table 3.1) in all the formulation and the friability value is less than 1% which ensures that formulated tablets were mechanically stable. The bathes LS-2, LS-5, LS-6, LS-8, LS-9, LS- 11 showed best results as it had perfectly optimized concentration of binder and disintegrant while the rest batches had very less or very high concentration of either material and hence showed varied results.

4.3 Weight variation:

The maximum % deviation was found to be ± 0.9% from all the formulations. As none of the formulation showed a deviation of more than ± 7.5% (USP limit) for any of the tablets tested, the prepared formulations comply with the weight variation test thus it fulfills the USP requirements

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4.4 Uniformity of drug content:

The drug content in different tablet formulations was highly uniform and in the range of 94 to 99% (Table 3.1). The maximum % drug content for all the formulation was found to be 99.0% It is in the limits specified by IP. Batches LS-2, LS-5, LS-6, LS-8, LS-9, LS-11 showed best results.

4.5 Disintegration time:

The time required for disintegration of six tablets, placed in each tube of disintegration test apparatus, was measured at 37±2°C using 900 ml of pH 6.8 phosphate buffer. Minimum disintegration time was 10 sec and maximum was 25 sec. Batches LS -2, LS-5, LS-6, LS-8, LS-9, LS- 11 showed best results as it has perfectly optimized concentration of binder and disintegrant while the rest batches had very less or very high concentration of either material and hence showed varied results.

4.6 In vitro drug dissolution study:

The drug release rates of Liquisolid compacts were distinctly higher as compared to directly compressed tablets, which show significant benefit of Liquisolid in increasing wetting properties and surface area of drug available for dissolution. From *in vitro* drug dissolution profile of Fenofibrate liquisolid tablet, it was found that 82-83% of the drug was released within 6 hours in LS -2, LS-5, LS-6, LS-8, LS-9, LS- 11 the formulation.

4.7 Stability study:

The pure Fenofibrate tablets were charged on accelerated stability and monitored for appearance, content and in-vitro dissolution study at 1,2 and 3 month. The obtained data were mentioned in table. The stability study reveals no significant variation in appearance, content and in-vitro dissolution study of pure Fenofibrate tablets up to three months.

TABLE NO 4.1 - KINETICS OF DRUG RELEASE (Liquisolid tablets of Fenofibrate):-

S.NO	kinetic parameter	Batch no-2		Batch no-5		Batch no-6		Batch no-8		Batch no-9		Batch no-11	
1		R	K	R	K	R	K	R	K	R	K	R	K
2	ZeroOrder	0.7928	10.1212	0.7598	10.8505	0.6993	12.7488	0.7308	10.5996	0.8527	12.6262	0.9088	13.6970
3	T-test	1.840	(Passes)	1.653	(Passes)	1.384	(passes)	1.514	(Passes)	2.309	(passes)	3.081	(passes)
4	FirstOrder	0.8081	0.1156	0.7740	0.1252	0.7077	0.1514	0.7413	0.1218	0.8784	0.1502	0.9336	0.1668
5	T-test	1.940	(Passes)	1.729	(Passes)	1.417	(passes	1.562	(passes)	2.599	(passes)	3.684	(passes)
6	Matrix	0.9625	16.0950	0.9494	17.3160	0.9241	20.4687	0.9381	16.9689	0.9767	19.8947	0.9826	21.3446
7	T-test	5.017	(Passes)	4.274	(Passes)	3.419	(passes)	3.829	(passes)	6.432	(Passes)	7.481	(Passes)
8	Peppas	0.9873	20.5451	0.9982	22.9841	0.8989	28.6889	0.9965	23.0873	0.8896	24.0744	0.8640	23.6129
9	T-test	8.797	(Passes)	23.385	(Passes)	2.901	(passes)	16.943	(Passes)	2.755	(passes)	2.427	(passes)
10	Hix crow	0.8030	0.0368	0.7692	0.0398	0.7048	0.0467	0.7377	0.0387	0.8699	0.0472	0.9260	0.0520
11	T-test	1.905	(Passes)	1.702	(Passes)	1.405	(passes)	1.545	(passes)	2.495	(passes)	3.469	(passes)
12	Best fit model	Peppas n=0.1767,k=20.5451		Peppas n=0.1221,k=22.9841		Matrix n=0.0453,k=28.6889		Peppas n=0.0877,k=23.0873		Matrixs n=0.2442,k=24.0744		Matrixs n=0.3570,k=23.6129	

CHAPTER-5
CONCLUSION

This novel technique is found to be efficient method for formulation of water insoluble solid drugs andliquid lipophilic drugs. Rapid disintegration rates are observed compared to conventional tablets and therefore, they show improved release rates and hence greater bioavailability. The use of nonvolatile solvent in the formulation causes increased wettability of water insoluble drugs and ensures molecular dispersion of drug in the formulation. Modification of formulation by use of certain agents cause sustained release of drugs from the liquisolid tablets. Liquisolid Formulations shows better Flowability, Compressibility, improves solubility, Dissolution and hence better absorption.

The liquisolid tablet technique can effectively enhance dissolution rates of poorly water-soluble drugs such as **fenofibrate**. Liquisolid technique gives a design to enhance the absorption as well as dissolution rate their by it may enhance the bio availability of a poorly soluble, insoluble or lipophilic drug and to formulate them into immediate release or else sustain release by selection of suitable solvent and carrier. In this technique drug is dissolved in a non volatile solvent and their by this liquid medicament is converted to non adherent, dry looking and free flowing by using suitable carrier and coating material. Because of the presence of drug in the state of solubilised or moleculary dispersed state, so solubility of insoluble drug is enhanced. The use of non-volatile solvent causes increased wettability and ensures molecular dispersion of drug in the formulation .

It is well established that the inadequate dissolution of water-insoluble drugs is the major reason for their poor and erratic bioavailability since it is the rate determining step in the absorption of nonpolar molecules. Liquisolid formulations were designed to contain liquid medications in powdered form, thereby possessing mechanisms of drug delivery similar to those of soft gelatin capsule preparations containing liquids. The liquisolid technique could be a promising alternative technique to increase the dissolution of water insoluble drugs and thereby enhance their absorption characteristics.

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